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NEW SERIES

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ORIGINAL ARTICLES

CARCINOMA OF THE LUNG*

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SINCE the first pneumonectomy for carcinoma of the lung was successfully performed by Graham in 1933, more and more importance has been placed on early diagnosis of that condition. As its medical treatment has nothing to offer, and as irradiation therapy is utilized only as a palliative procedure, surgery remains the only means by which the disease can be eradicated and a cure effected.

An analysis of the cases of carcinoma of the lung that have come to operation on the Chest Division of Bellevue Hospital between 1939 and February 1946 has, therefore, been made to help the physician evaluate this disease more correctly.

This series of 70 consecutive cases of carcinoma that have been explored surgically for removal composes 20% of all cases of carcinoma of the lung that were seen on the Chest Division during this time. The other 279 cases that did not come to operation were considered to have passed the stage of operability at the time that the diagnosis was made or suspected, with the exception of a few that refused operation. Of the 279 cases that were inoperable, 150 were proved by pathologic examination, 129 were suspected of having carcinoma. Of the 279 patients not com-

ing to operation, 91 (32.6%) died in the hospital. In 23% the diagnosis was not proved by pathologic section, as autopsy was refused. Therefore, of 349 cases of carcinoma of the lung approximately 80% had failed to have their diagnosis made by physicians at a time when the disease was sufficiently localized to remove. Of the 20% that were explored, 25 cases were resectable, an operability of only 7.2% of the 349 patients on whom the diagnosis was made. The importance of early diagnosis is therefore obvious.

The 70 cases that came to operation included all cases in which it was felt that a reasonable chance of success for resection of the carcinoma existed. In cases in which the resectability was questionable, the benefit of the doubt was given the patient and he was explored. Cases in which cerebral, liver or extensive bone or lymph gland metastasis had already occurred were not explored. Patients that were moribund or semi-comatose were also not considered candidates for exploration. The presence of pulmonary suppuration, lung abscess and empyema, however, did not predicate against removal of a malignant process, although

* Expenses for this study were partly defrayed by a grant from the Mary Robinson Lambert Foundation, Inc.

the prognosis of such cases was less favorable.

In the last 10 years, because of the tremendous strides that have been made in anesthesia, the hazards of pulmonary resection have been markedly decreased. Routine employment of a closed intratracheal system enables the surgeon to operate deliberately and without the fear that the patient may not survive because of the difficulty in breathing in the presence of an open chest. In addition to this, the training of anesthetists in the importance of frequent suction during operation and close coöperation between the anesthetist and the surgeon in evaluating the patient's condition have permitted the surgeon to complete his operation and keep his patient in the best possible condition.

As a result of the operative experience on the Chest Division, the attitude is tending more and more toward early exploration of cases with only suggestive Roentgen ray findings and with possibly no other evidence of disease. It is only by careful appreciation and correct evaluation of the importance of negative evidence, such as negative history and negative bronchoscopic examination, that early carcinoma will be diagnosed at a time when the patient can be cured of his disease.

Bronchoscopy was performed on these patients on the Chest Service by the resident staff under the direction of Drs. Kernan, Cracovaner and Wolcott. This is part of the Chest Surgical Division and its importance in treatment and diagnosis cannot be overestimated. This series represents all those cases operated on by 8 surgeons on the Division.

Clinical Data. OPERATION. The series represents a total of 70 cases that were explored for resection of carcinoma of the lung, 25 of which were resectable and 45 of which were non-resectable. Of the resected cases, pneumonectomy was performed in 20 of 25 cases (80%); lobectomy was utilized in the remaining 20%; 16 of

the 25 cases of resection were on the right side and 9 on the left side; 27 of the non-resectable cases were on the right side and 18 on the left.

SEX. As in other reported series, the predominance in males is striking. Of the 70 patients explored, 68 (97.1%) were men. Of these, 61 were white, 4 were colored, 2 were Chinese and 1 was Turkish.

AGE. The average age of patients explored was 52.8 years, the resectable cases being approximately the same age as the non-resectable. Age in itself was not considered a contraindication to exploration. The oldest patient explored was 70 years of age and had a non-resectable carcinoma. One patient, aged 66, however, proved resectable. The youngest patient who underwent resection for his carcinoma was 37. These data bear out the fact that this disease affects a certain percentage of patients under 40 years of age. Likewise, as 64% of resectable cases occurred between 50 and 70 years of age, the popular conception that pulmonary resection is contraindicated in the older age groups is not substantiated.

STAY IN HOSPITAL. The average stay of all patients in the hospital from time of admission to discharge was 87 days. The average period from admission to exploration was 40 days, being 41 days in the resectable cases and 37 days in the non-resectable. During this time, the patients, if possible, had their diagnosis established with biopsy at bronchoscopy. Frequently, exploration was made where biopsy was negative and bronchoscopy was suggestive. A rigid or narrowed bronchus or an angulated bronchus was considered suggestive evidence in those cases in which biopsy was not obtainable. An attempt was made in all cases to diminish the sputum as much as possible before exploration, in view of the stormy postoperative course that so frequently characterizes a case with a large amount of sputum. Courses of sulfadiazine and penicillin, and occasionally oxygen therapy administered by high concentration oxygen mask, were adjuvants in reducing the amount of

sputum and in affecting its anaërobic flora, thus converting its character from foul to non-foul variety.

Because of the importance of early diagnosis for early exploration, it is of interest to consider the cause for delay in 9 patients of the 70 that were explored. These patients were kept in the hospital on an average of 96 days before exploration. Five of the 9 cases were resected and 4 were non-resectable. Of the 9 cases, 6 had negative bronchoscopic findings on the first examination. In 3 of the 6 cases diagnosis was delayed until bronchoscopy was performed a second time, yielding a positive biopsy. In these 3, because of failure to make an early diagnosis, the tumors were allowed to progress until they were visible by the bronchoscope.

The extent that the tumors progressed outside the bronchus during the 6 week interval between bronchoscopies cannot be determined. It is known, however, that at operation 1 of these cases had advanced into the mediastinum sufficiently far to prevent its being resected. The other 2 were successfully resected, but that extension might have occurred in the interval is suggested by the fact that 1 developed recurrent nodes in the neck 3 years after operation and the other died of the continued extension of his disease 8 months after resection. In neither of the latter 2 cases had any extension of the disease been appreciated at operation. Of the 3 cases with positive or suggestive bronchoscopic findings, 1 was psychotic on arrival which delayed his study; 1 had Type III pneumococcus pneumonia on admission which masked the diagnosis; and the third had poor pulmonary function, low pulmonary reserve and an old posterior infarct of the heart, all of which required evaluation before subjecting him to pneumonectomy. The latter case proved resectable. In 6 of the 9 cases no wheeze was detected, which, when present, so frequently suggests the diagnosis. This emphasizes the importance of not depending on the presence of a wheeze for diagnosis or waiting until it develops before

advising exploration. Of the 4 non-resectable cases, there was delay in 1 by reason of preoperative irradiation therapy. Another of the 4 was in the hospital 5½ months before exploration; the first bronchoscopy yielded a negative biopsy and 3 thoracotomies for empyema preceded the exploration.

Earlier diagnosis would have brought all 9 patients to an earlier exploratory operation, and in case of the 4 non-resectable tumors there is a possibility that obviating the delay would have allowed the surgeon to remove the tumor.

During the 7 year period of this study (1939 to February 1946), the cases have been fairly evenly divided over the years. The record of resectability is a little better in the recent years: there were 14 resectable and 32 non-resectable cases in 1939 to 1943 inclusive, and 11 resectable and 13 non-resectable cases since then.

SYMPTOMS. The 70 cases undergoing exploration were analyzed according to the symptoms which they had on admission to the hospital (Table 1). Comparison of the symptomatology in those cases which were resectable and those which were non-resectable shows how little help the symptoms give in evaluating the resectability of carcinoma of the lung. Hemoptysis and wheeze were less frequent in resectable tumors than those which were non-resectable. Almost half of the cases, however, without wheeze proved inoperable at operation so that too much emphasis cannot be put upon this symptom.

The duration of symptoms before admission to the hospital again has been estimated according to the resectable and non-resectable cases, those undergoing resection averaging 9 months, 10 days, and those undergoing exploration only averaging 7 months, 7 days. That this indicates that the type of tumor is slower growing in the resectable type is open to question.

In evaluating the sputum of the cases at admission, the difference again was not appreciable between the cases that were resectable and those that were non-resect-

able. Ten (50%) of the resectable cases had over 6 ounces of sputum daily and 14 (66%) of the non-resectable cases had as much as 4 ounces of daily sputum. As a criterion of resectability, therefore, the presence or absence of sputum is of little value.

tumor is centrally located and intrabronchially visible. But a negative bronchoscopic examination calls for exploration if the tumor by Roentgen ray is peripherally located or in the upper lobes.

The symptoms of all cases has been classified according to whether broncho-

TABLE 1.—INCIDENCE OF SYMPTOMS IN RESECTABLE AND NON-RESECTABLE LUNG CANCERS COMING TO OPERATION

	No. cases	Cough	Blood	Pain	Wheeze	Loss of weight	Av. weight loss, lbs.
Resectable	25	23 (92%)	12 (48%)	15 (60%)	6 (24%)	18 (72%)	26.7
Non-resectable	45	41 (91.1%)	36 (80%)	34 (75.6%)	23 (51.1%)	33 (73.3%)	22.6
Total—all cases explored	70	64 (91.4%)	48 (68.6%)	49 (70%)	29 (41.4%)	51 (72.9%)	24.2

TABLE 2.—SYMPTOMS IN RELATION TO BRONCHOSCOPIC BIOPSY FINDINGS

Biopsy findings	No. and % of cases	Av. duration of symptoms	Type and incidence of symptoms				
			Cough	Blood	Pain	Wheeze	Loss of weight
Positive	36 (57.1%)	8 mos. 28 days	34 (94.4%)	25 (69.4%)	25 (69.4%)	15 (41.6%)	30
Suggestive	11 (17.5%)	7 mos. 22 days	10 (90.9%)	10 (90.9%)	9 (81.7%)	6 (54.5%)	6
Negative	16 (25.4%)	5 mos. 25 days	14 (87.5%)	9 (56.3%)	11 (68.8%)	6 (37.5%)	10

BRONCHOSCOPY. As a positive diagnosis of carcinoma is made by biopsy at bronchoscopy, the importance of bronchoscopic examination is paramount as a single diagnostic procedure. Of the 63 cases in this series bronchoscoped at Bellevue, 36 (57.1%) had a positive biopsy. Suggestive bronchoscopic findings were present in 11 (17.5%); in 16 (25.4%) bronchoscopy was completely negative.

Of the 16 cases with completely negative bronchoscopy, 7 (44%) were resectable. Of the 36 cases with positive biopsy, 13 (36%) were resectable. Of the 11 cases with suggestive bronchoscopy but without positive biopsy only 2 (18%) were resectable. This emphasizes the importance of evaluating negative bronchoscopic examination in the presence of positive Roentgen ray findings. Obviously the resectability of carcinoma of the lung depends on early exploration of cases with suggestive Roentgen ray changes, even though bronchoscopic findings are negative.

Bronchoscopy is very helpful if the

scopic biopsy findings were positive, suggestive or completely negative. A study of Table 2 shows that patients with positive biopsy findings had had symptoms on an average of 3 months earlier than in those with negative findings.

Of the 63 cases bronchoscoped at Bellevue Hospital, the average time from admission to exploration was 39.6 days. These cases have again been divided into those that underwent a single bronchoscopy and those cases that required 2 and 3 bronchoscopies before coming to operation. An analysis of these cases shows that those in which it was found necessary to bronchoscope twice underwent a much longer period from the time of admission to the time of operation than those which had only required 1 bronchoscopy. In the cases in which bronchoscopy was negative on the first examination the duration before operation was obviously the longest. Negative bronchoscopic findings deserve little consideration if the

diagnosis is suspected for other reasons, especially Roentgen ray findings.

In Table 3, the patients coming to operation have been classified according to bronchoscopic findings, operative procedure and side of lesions. A higher incidence of right-sided lesions was present, approximately the same percentage of those resectable being on the left side as on the right. Lobectomies were performed only in those cases having completely negative bronchoscopic findings. In 1 case in which upper lobectomy was performed the blood supply to the lower lobe was embarrassed, which resulted in poor function postoperatively and was

plemented with ether in 5; and gas, oxygen and ether in 4.

The average operating time on all cases was 2 hours, 8 minutes; anesthesia time was 2 hours, 39 minutes. The average operating time in resectable cases was 3 hours, 25 minutes, and in the exploratory thoracotomies without resection 1 hour, 26 minutes. The anesthesia time was correspondingly longer in both groups.

In the operative repair of the stump in the resected cases silk was used in most cases, with individual ligation and silk technique in 80 % of cases.

POSTOPERATIVE COMPLICATIONS. Of the 70 patients explored, 5 died within 2 days

TABLE 3.—CLASSIFICATION OF PATIENTS ACCORDING TO BRONCHOSCOPIC FINDINGS AND OPERATIVE PROCEDURES

	Total	Exploratory thoracotomy		Pneumonectomy		Lobectomy		Av. preoperative time in hospital (days)
		Right	Left	Right	Left	RUL	LUL	
Bronchoscoped once:								
Positive biopsy	27	14	6	6	1	34.8
Suggestive bronchoscopy, negative biopsy	10	5	3	1	1	35.6
Negative bronchoscopy	11	3	3	1	..	2	2	36.0
Bronchoscoped twice:								
1st negative, 2nd positive biopsy	4	1	..	2	1	104.0
1st negative, 2nd negative	5	2	1	1	..	1	..	50.2
1st suggestive, 2nd positive biopsy	4	..	2	1	1	34.0
Bronchoscoped 3 times:								
1st negative, 2nd suggestive, 3rd suggestive	1	..	1	58.0
1st suggestive, 2nd suggestive, 3rd positive	1	1	38.0
Totals	63	25	16	12	5	3	2	39.6

attended by failure of complete reëxpansion. Whether lobectomy is justifiable for carcinoma or not is debatable. It is the consensus that if a patient has a carcinoma and can stand the loss of pulmonary parenchyma, pneumonectomy is preferable to lobectomy. If, however, the disease is well localized to 1 lobe of the lung with completely negative hilar glands, lobectomy may be the operation of choice.

OPERATIVE DATA. The total number of cases explored was 70, of which 25 were resectable and 45 non-resectable. Pneumonectomy was employed in 20 cases (80 %) and lobectomy in 5 (20 %).

The operative approach was anterior in 47 (67.1 %), posterolateral in 17 (24.3 %) and lateral in 6 (8.6 %). In the resectable cases the anterior approach was used in 17 (68 %), the posterior in 8 (32 %).

The anesthetic agent used in 64 cases was cyclopropane in 55; cyclopropane sup-

following operation. In 60 of the remaining 65, the wound healed by primary union, an incidence of 92.3%; 3 (4.6 %) had serious wound infections; 1 had a mild wound infection and 1 a previously undiagnosed abscess which was drained following exploratory thoracotomy for resection. Of the resected cases, 95.5 % healed by primary union. There were 1 serious infection and 3 deaths within 2 days following operation. Pleural infection developed in 9 of the resected cases, or 41 % of all cases surviving the first 2 days. Brouchopleural fistulæ developed in 4 of the resected cases (18 %); in 77 % fistula did not develop; in 5 % it was questionable. The total percentage of pleural infections in resected and non-resected cases was 21.5.

Collapse of the chest wall by thoracoplasty was performed in 4 of the resected cases. One patient was successfully oper-

ated upon 7 months after pneumonectomy for relief of symptoms due to mediastinal shift. In the other 3 cases operation was performed for infection to obliterate the residual space $3\frac{1}{2}$ months, 6 months, and 2 years, respectively, after resection. Eight of the 25 resection cases underwent thoracotomy, either at the time of operation or during the postoperative course. In 1 patient dyspnea developed after an interval during which there developed a thickening of the parietal pleura sufficient to prevent collapse by thoracoplasty. In this case oil was used to stabilize the mediastinum. The choice of cases for collapse was based on symptoms and on the patient's ability to withstand addi-

on section completely different types of tumor, although gland formation was predominant. This case was inoperable and is included in the non-resectable group.

In the total group of 70 cases, 10 had insufficient evidence for complete pathologic classification. These were all in the inoperable group and represent cases in which specimens for biopsy were not taken at operation or where adequate tissue reports were not available. Because of these 10 cases that could not be classified, the percentage of individual tumor groups that were resectable is incomplete. However, it is of interest that 75% of known adenocarcinomas were resectable, whereas

TABLE 4.—ANALYSIS OF OPERABILITY IN RELATION TO TYPE OF TUMOR

Type	Total No. and % of cases	No. and %		Type resectable (%)
		Resectable	Non-resectable	
Adenocarcinoma	8 (11.4%)	6 (24%)	2 (4.4%)	75.0
Squamous cell	28 (40.0%)	11 (44%)	17 (37.8%)	39.3
Undifferentiated cell	23 (32.9%)	8 (32%)	15 (33.3%)	34.8
Adenocarcinoma and squamous	1 (1.4%)	..	1 (2.2%)	0
Insufficient evidence to classify	10 (14.3%)	...	10 (22.2%)	
Total	70	25	45	

TABLE 5.—CORRELATION OF SYMPTOMS WITH TYPE OF TUMOR

Type	Average duration before admission	Cough (%)	Bleeding (%)	Pain (%)	Wheeze (%)	Loss of weight (%)	Sputum (%)
Adenocarcinoma	8 mos. 23 days	66.6	33.3	66.6	55.6	77.8	55.6
Squamous cell	9 mos. 3 days	92.9	89.3	89.3	32.1	82.1	82.1
Undifferentiated cell	6 mos. 2 days	91.3	73.9	65.2	52.2	73.9	65.2

tional surgery. In general, it is felt that if thoracoplasty is to be performed it should be done at an early date before pleural thickening has developed.

PATHOLOGIC FINDINGS. In Table 4 are listed the types of tumor found and their several records of operability. The squamous variety composes the most frequent carcinoma encountered, comprising 44% of resected and 37.8% of non-resectable tumors. The undifferentiated tumors compose 32% of the resectable and 33.3% of the non-resectable groups; whereas adenocarcinoma was encountered in 24% of resected tumors and only 4.4% of the non-resected tumors. In 1 case elements of both adenocarcinoma and squamous cell carcinoma were present, suggesting

only 39.3% of squamous and 34.8% of undifferentiated tumors were removable.

In Table 5 the symptoms have been arranged according to the nature of the tumor. The case containing both glandular and squamous cells has been listed with the adenocarcinomas to which it predominantly belongs. Cough and bleeding are much commoner in the squamous and undifferentiated cell groups than in the adenocarcinomas, whereas wheeze was noted less frequently and pain more often in the squamous tumors. The average duration of symptoms before admission to the hospital was 2 months less in the undifferentiated group than in the other 2 types of tumor.

That the duration of symptoms is of

no use in determining resectability in the undifferentiated group is shown by the fact that 28.6% of undifferentiated carcinomas with symptoms for less than 4 months were resectable, whereas 44.4% with symptoms over 4 months were able to be resected. The significance of early diagnosis to permit early operation lies in the fact that the tumor when first seen may be so far advanced that any delay will be just enough to prevent resection.

carcinomas with positive biopsy had bleeding. The significance of this finding is modified somewhat by the small number of adenocarcinomas that had a positive biopsy.

A summary of the follow-up of the 3 pathologic groups is included to show the survival time in relation to the type of tumor. As would be expected, the squamous tumors are slower growing and in this group longevity was the greatest. In

TABLE 6.—CORRELATION OF RESECTABILITY WITH TYPE OF LESION AND RESULT OF BRONCHOSCOPIC BIOPSY

Type	Positive biopsy		Negative biopsy		Positive biopsy (%)	
	Resectable	Total	Resectable	Total	Resectable	Total
Adenocarcinoma	1	2	5	6	16 6	25 0
Squamous cell	8	20	2	7	80 0	74 1
Undifferentiated cell	5	15	2	6	71 4	71 4
Adenocarcinoma and squamous cell	1	100 0

TABLE 7.—SURVIVAL TIME FOLLOWING OPERATION OF 40 KNOWN DEAD

Postoperative interval before death	Resected	Non-resected
1st month	7	4
1 to 6 months	3	5
6 mos. to 1 yr.	2	9
1 to 2 yrs.	3	3
2 to 3 "	0	1
3 to 4 "	0	0
4 to 5 "	0	1
Over 5 yrs.	1	0
Date of death unknown	1
Totals	16	24

The age incidence of the several types of tumor was within 4 years of each other, with the squamous tumors averaging 53.6 years, the undifferentiated group 49.6 years, and the adenocarcinomas 51.7 years.

In evaluating the diagnostic value of bronchoscopy in relation to the type of tumor present, the resectability of adenocarcinoma was to a high degree associated with negative biopsy, whereas the resectable squamous cell and undifferentiated cell tumors were more frequently able to be biopsied (Table 6).

Correlating the cases that had positive biopsy with those that bled, it is found that both undifferentiated and squamous cell groups had approximately 57% with both findings, whereas 11% of the adeno-

the *undifferentiated cell type* group there were 8 patients who had resection; of these, 4 lived over 12 months, 2 over 24 months and 1 over 56 months. Of 15 patients in this group who did not have resections, only 8 could be followed, and of these 3 lived over 6 months, 1 over 12 months and none over 24 months. In the *squamous cell type* group there were 11 patients who had resections and 10 could be followed. Of these, 5 lived over 6 months, 4 over 12 months, 2 over 36 months, and 1 over 60 months. Of 17 patients in this group who did not have resections, 11 could be followed, and of these, 7 lived over 6 months, 2 over 12 months, 1 over 48 months, and none over 60 months. In the *adenocarcinoma* group, of 6 patients who had resections, 3 were followed, and

of these, 1 lived over 6 months and none over 12 months. Of 2 patients in this group who did not have resections, the one who could be followed lived over 48 months.

MORTALITY. Of the 70 patients operated upon, 17 died in the hospital, a mortality of 24.3%. This is somewhat lower than the 32.6% mortality of the 279 non-operated cases that died on the service during the same time. Of the resected cases, 10 died in the hospital, a hospital mortality of 40%; 7 of the 10 cases died during the 1st month (28%) which represents the operative mortality. Of these resected cases dying in the hospital, 1 died in the first 24 hours, 4 in the 1st week, 7 in the 1st month, and 3 in 2 to 6 months after operation. Of the pulmonary resection cases, 16 of the 25 (64%) are known to be dead. Of 9 cases not known to be dead, 4 had no follow-up after leaving the hospital; 5 had follow-up and averaged 20 months postoperative when last seen.

Of the non-resectable cases, 7 died in the hospital, a mortality of 15.6%. Two died in the hospital in the first 24 hours, 2 more in the next 30 days, and 3 after 1 month postoperatively. Of the non-resectable cases, 24 are known to be dead (53.3%). Of the 21 cases not known to be dead, 16 had no follow-up after leaving the hospital, 5 were seen in follow-up and averaged a period of 16 months. Of these, 1 was seen at 52 months, having had large doses of Roentgen ray therapy.

An analysis of the causes of death of those patients dying in the hospital is of interest. Three of the 10 resected cases developed fistulae which were not recognized sufficiently early to prevent the patients emptying the contents of the pleural space into the bronchial tree. In this regard an attempt is made technically at operation to pleuralize the bronchial stump. A single layer of interrupted silk sutures to close the end of the bronchus may or may not be reinforced with loosely applied mattress sutures proximal to this layer to approximate membranous portion of bronchus posteriorly to car-

tilaginous portion anteriorly. Before the chest is closed, saline solution is introduced into the pleural space and positive pressure applied to the bronchial tree by the anesthetist in order to demonstrate any possible leak that may still remain. If this is present, further sutures are applied to close the bronchus at this point.

Three fistulae that developed in resections occurred on the 7th, 13th and 23rd days postoperatively. In 2 of these the fistula was the direct cause of death. In the third, the patient also had an empyema and an acute fibrinopurulent pericarditis which contributed to the patient's death. In all 3 the pleural space should have been drained earlier. In pneumonectomized patients, a sudden rise in temperature even after 3 weeks must be regarded with suspicion. Coughing and raising blood-tinged brownish red sputum postoperatively, especially after a free interval, is an immediate indication for emergency drainage of pleural cavity by thoracotomy. Makeshift needle aspiration and closed intercostal drainage should be employed only as a short preliminary to open operation. The failure to recognize the urgency of open drainage will result fatally for the patient.

One death on the table from hemorrhage occurred in a patient whose carcinoma was associated with considerable pneumonitis that resulted in a solid lung with failure of the lung to collapse more than 20% on opening the chest. The mediastinum was thickened and edematous, the blood-vessels friable and in tying the pulmonary vein with silk suture slipped off. Because of poor exposure it was difficult to control the hemorrhage and in attempting to do so a portion of the auricle was torn and the patient succumbed.

The technical difficulties of resection in the presence of similar lesions is obvious. One technical maneuver has since been used in similar cases where the vein is short as a means of preventing the silk tie from slipping. This includes the use of transfixion sutures through pericardium and vein proximal to clamps placed on the

vein which will then allow a running continuous stitch to close vein and pericardium together.

The fifth death that could possibly have been prevented was in a patient who had a large amount of secretions postoperatively. He had raised about $\frac{1}{2}$ cup of thick yellow sputum before operation and died on the 2nd postoperative day before bronchoscopy was done. Cases such as this have led us to believe that all "moist" cases should have bronchoscopy on the table postoperatively, irrespective of how recently the patient has been aspirated through an endotracheal tube by the anesthetist. Frequently bronchoscopy done 10 or 15 seconds after relatively dry endotracheal aspiration will reveal the main bronchus on the opposite side filled with secretions and occasionally the stump on the operated side also containing moisture.

After the patient has returned to his bed, secretions are reduced by cough with pressure and by endotracheal suction with rubber catheter introduced at intervals through larynx into trachea. When this is unsuccessful and the patient becomes embarrassed from endotracheal secretions, he should be bronchoscoped in bed, after the application of a small amount of cocaine to the posterior pharynx and the pyriform sinuses on each side to facilitate passage of the bronchoscope. In this respect the adeptness of the resident staff with the passage of a bronchoscope is an important part in the postoperative treatment.

A prophylactic course of chemotherapy is routinely employed to reduce preoperative sputum, and similar therapy is instituted postoperatively. Lately, sulfonamides have been replaced by penicillin, although these are occasionally combined for maximum effect.

Of the other 5 hospital deaths in resections, 3 were due to extension of the disease, either direct or metastatic. One patient died of jaundice from sepsis. Operation had been delayed $3\frac{1}{2}$ months while the patient's carcinoma had broken down and was eventually drained before

resection was attempted. In similar cases it is felt if diagnosis can be established excision is preferable to preliminary drainage. The 5th case was one of renal shutdown following transfusion reaction which occurred on the 2nd postoperative day.

Of the 7 deaths in non-resectable cases, 4 died of infection including empyema, contralateral bronchopneumonia and acute purulent bronchitis; 2 died of metastases, and 1 died of intrabronchial hemorrhage.

The survival times following operation of those patients known to have died are given in Table 7, both for resected and non-resected cases. Of both groups only 1 resected case survived 5 years after operation, which represents 1.4% of the entire series, or 2.6% of the total cases that were operated upon more than 5 years ago.

RESULTS OF IRRADIATION THERAPY. Of the 70 patients who were explored for carcinoma, 21 had irradiation therapy. Of these, 13 (61.9%) are known to be dead. Three of the 21 cases given Roentgen ray treatment were resections, its use in these cases being to control pain rather than to control the extension of the disease. The average survival time of the 3 resection cases was $9\frac{1}{2}$ months.

Of the 18 non-resectable cases given Roentgen ray treatment, 10 were followed to death and averaged 15 months following operation. Two patients given Roentgen ray, who have been seen postoperatively but are not known to be dead, were seen $11\frac{1}{2}$ and 52 months after operation.

The value of irradiation has never been fully determined, nor is it possible in this series to evaluate its effect. The main point to decide is whether or not irradiation has prolonged life expectancy in those cases that were inoperable. As the cases differ widely in the type and extent of the growth, the effect of irradiation is difficult to assess. However, in the group that was explored but not resected, an accurate means of determining the extent of the disease present in these cases was afforded by operation, so that it is felt of value to analyze the records of the irradi-

ated and the non-irradiated cases that were followed to the time of their death. Of all non-resected cases that were followed after leaving the hospital to the time of death, 9 had irradiation and 7 did not. Follow-up on these 2 sets revealed the irradiated group survived an average of 14 months and 27 days and the non-irradiated group 7 months and 21 days. These figures would lead to the conclusion that Roentgen ray therapy had increased life expectancy. However, the conclusion is not justified because of the difference in the type and extent of the lesions in the 2 groups. Three of the cases given Roentgen ray therapy had no metastatic involvement at all, 1 being considered inoperable because "the pulmonary veins were involved." In the second case there was "a mass posterior to the heart," and the third case had a mass in the hilum that was adherent to the superior vena cava. These 3 cases survived 36 months, 19 months and 48½ months, respectively.

Dividing the irradiated cases into (1) those with metastases, (2) those without metastases but with direct extension into mediastinum, diaphragm or chest wall, and (3) those without metastases or direct extension, it is found that Groups 1 and 2 each had survival time of between 7 and 8 months, whereas Group 3 averaged 34.5 months. The 1 case not included in the above 3 groups that had irradiation and postoperative empyema, died in the hospital after 3 weeks. At exploration there were present hilar nodes, mediastinal nodes and a mass posteriorly adherent to the pericardium. Of the non-irradiated cases without suppuration but with metastases, the survival time was 9 months. Three cases of the non-irradiated group had suppuration, including empyema in 2 cases, and pulmonary suppuration in 1 case. In this group the survival time averaged little over 5 months. All the non-irradiated cases that were followed to their death had metastatic involvement at exploration. It is evident that the presence of infection, either in the form of empyema or pulmonary suppuration,

will hasten the demise of the patient. Of the whole series of irradiated cases there is only 1 patient with metastatic involvement who survived 12 months and who seemed to improve following irradiation. Two patients, who are not known to be dead, were seen at 11½ months and 52 months postoperatively after irradiation. It was felt that the man who survived 52 months had in all probability been helped by irradiation because of the duration of survival following exploration. Both of the cases were squamous cell tumors with metastatic involvement at operation.

In summarizing the results of Roentgen therapy it is felt that it was useless in the large percentage of cases to which it was given. Perhaps some good effect was obtained in 2 or 3 cases. Irradiation therapy in a non-resected case of carcinoma of the lung that has been explored should be used judiciously. If irradiation is given in large amounts in a short period of time the ill effects of the irradiation will counteract any beneficial effect that the patient may receive from having his tumor exposed to Roentgen ray. It is much more important to preserve the patient's appetite and his general well-being than to expose him to an overwhelming dose of Roentgen ray that will result in anorexia and rapid loss of weight and a consequently earlier death. Whether irradiation should be employed after resection is a question that cannot be answered on the evidence of this series of cases, since the only patients who received Roentgen ray therapy were those who had developed pain following a recurrence of their disease process. These patients did not seem to be benefited by their Roentgen-ray treatment.

CRITERIA OF RESECTABILITY. In analyzing the pathology of non-resectable tumors in this series it is apparent that cases which in the early years of the study were not subjected to resection would have been considered operable in later years. In this series 2 cases were considered inoperable "because of hilar

node involvement" and 3 cases because of carinal or tracheobronchial node metastasis. As more experience was gained at the operating table with bronchogenic carcinoma an increasingly larger group were resected that had some involvement of the mediastinum in direct extension or lymph gland metastasis to carinal or tracheobronchial nodes.

Ideally, patients should come to exploration before any such extension has taken place. For those cases in which extension is present at operation a radical type of pneumonectomy is now performed to include, in addition to pneumonectomy, removal of mediastinal nodes up to and including the subaortic node on the left. On the right, by dividing the azygos vein and retracting the superior vena cava anteriorly, it is possible to clean out the mediastinal nodes up to the base of the neck. Radical pneumonectomy of this type is more formidable than simple pneumonectomy and is utilized for the cases in which delayed diagnosis has postponed exploration and allowed mediastinal extension to occur. In this respect, early operation will be more favorable for cure and, as the amount of surgery is less, the operative risk also will be correspondingly diminished.

It is often impossible to recognize by Roentgen ray studies that involvement beyond the lung has occurred. This is shown by the operative findings in our 45 cases that had no Roentgen ray evidence of extension but that proved inoperable on exploration. There were 10 (22%) with metastasis to pleura or chest wall, 30 (66%) with direct extension of the tumor into hilum, chest wall, diaphragm or mediastinum, 10 (22%) with metastasis to hilar nodes, and 21 (47%) with metastasis to mediastinal nodes.

Summary. This series of 70 cases of carcinoma of the lung surgically treated stresses the diagnostic criteria and the importance of early exploration. These 70 cases represent only 20% of the cases of lung cancer encountered on this service, and only 7.2% of the total cases were resect-

able. This low incidence of operability is associated with a discouragingly low record of 5 year survival: only 1 case.

The average duration of symptoms in patients coming to resection was over 9 months, due to failure of the physician to make a diagnosis and of the patient to appreciate the importance of early symptoms. A large percentage of patients who had resections died because of tumor beyond the resected area and too small to be recognized at operation. Therefore, delay in exploration allows fatal extension of the disease and is partly responsible for the low survival rate after resection.

The relatively high incidence of fistulae and of pleural infection in resected cases in this series indicates where improvement in operating technique and postoperative management is required.

Equally challenging to the surgeons is the correct handling at operation of the tumor and its possible extension into the mediastinum. Careful dissection and skillful handling of the mediastinum have enabled more cases to be resected. As each surgeon's criteria of operability become more inclusive, a more radical approach is being adopted toward the disease. Spread of the disease to the regional lymph nodes and mediastinum, following failure of early diagnosis, is now met by more radical resection with removal of lymph nodes and clearing out of the mediastinal glands up to the base of the neck. Success with this procedure has increased as further surgical experience has been attained. But the surgeon's attempt to make up for failure of early diagnosis by employing radical pneumonectomy entails a more formidable operation with a greater operative risk. The better way to lower mortality and increase the survival rate is earlier diagnosis and earlier exploration, permitting simple rather than radical pneumonectomy.

The operability of carcinoma cannot be predicted at bronchoscopy except that exploration is contraindicated in cases where the tumor can be seen to invade the trachea or extend to the opposite side.

Rigidity of a bronchus may be due to the suppurative factor associated with the tumor as much as to the growth and does not preclude exploration.

It is impossible to lay too much stress on the importance of Roentgen ray interpretation rather than bronchoscopy or

symptomatology for bringing about early exploration. Resectability is higher in cases with negative bronchoscopic findings. Until this fact is appreciated by the medical profession carcinoma of the lung will continue to have the hopeless prognosis that it has had in the past.

A STATISTICAL STUDY OF 112 CASES OF BENIGN GASTRIC ULCERATION

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In a recent 10 year study of 7300 gastro-intestinal examinations of civilian ambulatory patients with digestive symptoms, 1154 cases of duodenal ulcer and 112 cases of gastric ulceration were observed. The statistical study of the life cycle of duodenal ulcer has been reported in another publication.¹ In this communication the following statistical information of 112 cases of gastric ulceration will be given: (1) incidence of gastric ulcer, (2) site of the ulceration, (3) age and sex, (4) duration of symptoms, (5) symptoms and signs, and (6) recurrences.

For the purpose of this study two 5 year periods were selected—(1) prewar, 1937–1941, (2) wartime, 1941–1946—to determine what effect, if any, the war had upon the incidence of gastric ulceration.

In 7300 gastro-intestinal examinations in patients with digestive symptoms, peptic ulceration was found in 1266 cases. Of these, 1154 (86.7%) were duodenal and 112 (17.3%) gastric. For the purpose of this study, the gastric ulcer cases were divided into 2 groups, according to the site: Group 1, those involving the body and cardia, comprising 74 cases, and Group 2, those involving the pylorus, 38 cases.

Group 1. INCIDENCE. While the incidence of gastric ulcer, all sites, was 1.53%, that for involvement of the body and cardia was 0.84%. In a 5 year prewar period, 3500 gastro-intestinal examinations yielded 28 cases of gastric ulceration involving the body and cardia. In the second 5 year wartime period, comprising 3800 cases, 46 cases were observed. The prewar incidence was 0.8%, while the wartime incidence was 1.2%. The incidence increased 0.4% during the war in the civilian population. A similar increase was noted in the incidence of duodenal ulcer.

SEX AND AGE. Of the 74 patients with gastric ulcer, 60 were males and 14 females. The prewar group comprised 25 males and 3 females, the wartime group 35 males and 11 females. Comparing the two periods, there seemed to be a slight increase of females during the wartime period.

Table 1 shows that the majority of those who sought medical attention were between the ages of 30 and 70 years. It was of particular interest to observe the age of the patients at the onset of symptoms of gastric ulceration (Table 2). The onset occurred at an older age for those with gastric than for those with duodenal ulcer. The table shows a striking and significant difference in the age between the onset of symptoms in gastric and duodenal ulceration.

DURATION. The duration of symptoms ranged from 1 month to 40 years (Table 3). The majority of patients presented symptoms of from 1 to 10 years. Of particular interest is the number of cases of less than 1 year's duration seen during the wartime.

RECURRENCES. Recurrences with severe symptomatic episodes are not as common in gastric as in duodenal ulceration (Table 4). Of the 74 patients with gastric ulcer, the majority presented only 1 severe recurrence up to the time of the examination. There were 18 patients with acute ulceration seen during the wartime period, who had not had digestive symptoms before. A comparison between the 2 5 year periods showed an increase in the prevalence of acute gastric ulceration in the wartime group; otherwise there was little significant change.

SYMPTOMS AND SIGNS. All of the gastric ulcers were active and all showed an ulcer niche filling defect in the Roentgen examination. The predominant symptoms are shown in Table 5.

TABLE 1.—AGE AND SEX OF 112 PATIENTS WITH GASTRIC ULCER

	Ulcer of body and cardia				Pyloric ulcer			
	Males		Females		Males		Females	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
20-29 . . .	0	1	1	0	0	1	1	1
30-39 . . .	6	6	0	0	2	5	0	0
40-49 . . .	6	8	1	4	3	4	3	2
50-59 . . .	8	10	1	1	3	1	1	3
60-69 . . .	3	10	0	5	2	3	1	0
70-79 . . .	2	0	0	1	0	1	1	0
Total . . .	25	35	3	11	10	15	7	6

TABLE 2.—AGE AT ONSET OF SYMPTOMS IN 112 CASES OF GASTRIC ULCER

	Ulcer of body and cardia				Pyloric ulcer			
	Males		Females		Males		Females	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
16-20 . . .	1	0	0	0	0	0	1	1
21-25 . . .	4	0	1	0	3	1	1	1
26-30 . . .	2	4	0	0	1	4	0	0
31-35 . . .	3	3	0	2	0	1	1	0
36-40 . . .	3	8	1	1	1	2	1	1
41-45 . . .	2	4	0	1	2	2	0	2
46-50 . . .	4	7	1	1	0	1	2	0
51-55 . . .	2	3	0	0	0	0	0	1
56-60 . . .	1	0	0	3	1	3	0	0
61-65 . . .	1	5	0	1	2	0	0	0
66-70 . . .	0	1	0	2	0	0	1	0
71-75 . . .	2	0	0	0	0	1	0	0
Total . . .	25	35	3	11	10	15	7	6

TABLE 3.—DURATION OF SYMPTOMS IN 112 CASES OF GASTRIC ULCER

	Ulcer of body and cardia				Pyloric ulcer			
	Males		Females		Males		Females	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
1- 3 mos. . .	1	5	0	1	1	2	0	0
3- 7 " . . .	1	2	0	1	0	1	0	0
8-11 " . . .	1	4	0	1	1	0	0	1
1- 3 yrs. . .	4	11	1	2	2	5	2	1
4- 7 " . . .	4	3	1	3	0	4	2	1
8-11 " . . .	7	2	1	2	2	0	0	1
12-15 " . . .	2	4	0	0	2	3	0	1
16-20 " . . .	1	2	0	1	1	0	3	1
21-26 " . . .	3	0	0	0	1	0	0	0
27-34 " . . .	1	1	0	0	0	0	0	0
35-40 " . . .	0	1	0	0	0	0	0	0
Total . . .	25	35	3	11	10	15	7	6

TABLE 4.—RECURRENCES OF SYMPTOMS IN 112 CASES OF GASTRIC ULCER

	Ulcer of body and cardia				Pyloric ulcer			
	Males		Females		Males		Females	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
0 . . .	1	14	0	3	2	4	0	0
1 . . .	10	12	1	6	2	7	3	4
2 . . .	7	4	2	1	3	2	1	1
3 . . .	4	4	0	0	3	2	2	0
4 . . .	3	1	0	1	0	0	1	1
Total . . .	25	35	3	11	10	15	7	6

Pain. Of the 74 patients, 66 had pain; in 40 there was a history of food relation to the pain, it being worse after eating. A comparison between the two 5 year periods showed no change in the incidence of pain.

Vomiting. Vomiting occurred in 18 of the 74 cases. There was no change in the incidence of vomiting during the 2 periods.

Group 2. In 112 cases of gastric ulceration encountered in 7300 gastro-intestinal Roentgen examinations, 38 had pyloric ulcers situated at or close to the pyloric sphincter.

INCIDENCE. The incidence for this group was 0.52%.

SEX AND AGE. Of the 38 patients with pyloric ulceration, 25 were males and 13

TABLE 5.—SIGNS AND SYMPTOMS IN 112 CASES OF GASTRIC ULCER

	Ulcer of body and cardia				Pyloric ulcer			
	Males		Females		Males		Females	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Niche	25	35	3	11	6	13	6	6
Pain	19	33	0	8	0	5	2	4
Pain-food relation	12	22	3	3	7	8	2	0
Vomiting	7	7	1	3	3	10	4	2
Gastric hemorrhage	2	1	0	1	0	1	0	0
Black stools, exclusive of gastric hemorrhage	1	2	0	1	0	2	0	0
Pyloric obstruction	0	0	0	0	1	2	4	0
Perforation	2	0	0	0	0	0	0	0
Loss of weight	5	5	0	3	0	5	0	0
Diarrhea	0	0	0	2	1	0	0	0
Constipation	13	17	1	5	2	1	1	2
Bowels regular	9	14	2	3	1	0	1	0
Irritable spastic colon	0	0	0	2	4	4	4	2

Massive Gastric Hemorrhage. Massive gastric hemorrhage occurred in only 4 instances of the 74 cases of gastric ulceration. The incidence of massive gastric hemorrhage is rather low and is comparable with the incidence encountered in duodenal ulceration.

Black Stools. Although occult blood was observed in most of the cases, black stools was noticed by the patient in only 4 instances.

Perforation. Of the 74 patients, only 2 gave a history of perforation.

Loss of Weight. It is interesting to note that of the 74 patients, 16 complained of loss of weight. The loss of weight was due to abstinence of food.

Bowel Movements. Of the 74 individuals with gastric ulcer, 36 gave a history of constipation and 28 had regular bowel movements. In none of the cases were there Roentgen evidence of an irritable spastic colon. These findings differ considerably from those observed in duodenal ulceration, where a high percentage of irritable spastic colon is found.

females. Tables 1 and 2 show the incidence of sex according to age. The age of onset of pyloric ulceration varies considerably. The majority of pyloric ulcer cases were seen between the 3rd and 6th decades.

DURATION. The duration of symptoms varied from 1 month to 26 years (Table 3). It is interesting to note the small number of cases of short duration. The female group revealed only 1 case of less than 1 years duration.

SIGNS AND SYMPTOMS. Of the 38 cases of pyloric ulceration, 31 had an ulcer niche defect. The predominant symptoms were pain and vomiting. In this group of 38 cases, there was only 1 instance of massive gastric hemorrhage. The signs and symptoms are shown in Table 4.

OBSTRUCTION. Pyloric obstruction was observed in 7 instances.

RECURRENCE OF SYMPTOMS. Recurrences of symptoms in the 38 cases ranged from 1 to 4 (Table 5). There were 6 instances of males with a history of an acute

onset. In the females, there was none with an acute onset.

A comparison between the prewar and wartime groups revealed an increase in the percentage of acute and first recurrences of pyloric ulcerations during the wartime.

Summary. An incidence of gastric ulceration was 1.53% in a series of 7300 ambulatory patients with digestive symptoms. The ratio between duodenal ulcer and gastric ulcer was approximately 10 to 1. The incidence of gastric ulceration increased from 0.8 to 1.2% during the war

period. There was a slight increase of gastric ulcer in females during the wartime. Gastric ulcers of short duration or acute ulcers were more common during the wartime. Recurrences were less frequent in gastric ulceration, than in cases of duodenal ulcers.

There were 38 cases of pyloric ulceration among the 112 cases of gastric ulcers. The incidence of pyloric ulcer in 7300 gastro-intestinal examinations was 0.5%. The pyloric ulcers behaved like the gastric type, with the exception of a greater prevalence of obstruction.

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EXPERIMENTAL STUDY ON THE LOCALIZATION OF CASTLE'S INTRINSIC FACTOR IN THE HUMAN STOMACH

ANTI-ANEMIC EFFECT OF POWDERED HUMAN FUNDUS AND PYLORUS

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THE use of dried hog stomach, especially the pyloric portion, in the treatment of pernicious anemia is based on a number of clinico-therapeutic investigations demonstrating the effectiveness of this material.^{4,7,15} Preparations of the fundal portion of hog stomach were found to be inactive,^{7a,c,d,15} whereas pyloric preparations had a pronounced effect. Preparations made from the cardiac portion of the hog stomach and from the duodenum were also effective.^{7b,c,d} From his findings, Meulengracht^{7c} concluded that Castle's "intrinsic factor" was not produced by the fundal glands, but by the pyloric glands together with the cardiac glands and the duodenal glands of Brunner: the "pyloric glandular organ." Applying the results to pernicious anemia in man, Meulengracht concluded that the experiments indicated the site of the lesion in the stomach, and that in all probability pernicious anemia was due to atrophy and the inactivity of the "pyloric glandular organ."

From experiments with resection of the fundus of the stomach in hogs, Petri and his co-workers^{11,12,13} concluded that "the fundus is that region within the stomach which is primarily decisive as to . . . the formation of the anti-pernicious anemia principle."

However, repeated histologic studies on the human stomach in cases of pernicious anemia have shown that it is the fundal portion that undergoes the most conspicuous changes.^{1,6,7c,16} These changes are of an atrophic and degenerative character, increasing to total loss of specific glandular

elements in the fundal zone. The area of pyloric glands is either unchanged or presents some less pronounced changes.¹⁶ Also, gastroscopic examinations on patients with pernicious anemia indicate that it is the body of the stomach, the zone of the fundal glands, that is particularly affected.^{3,14}

Because of the discrepancy between the localization of the degenerative processes in the stomach in pernicious anemia and Meulengracht's view of the pyloric gland organ as presumably the most important source of the "intrinsic factor" in man, Fox and Castle² reinvestigated the site of intrinsic factor production. They were able fully to confirm the effectiveness of preparations of the pyloric portion of hog stomach and the lack of activity of preparations from the fundal portion, and support the assumption that this distribution of the anti-pernicious anemia activity is an indication of the site of secretion of the intrinsic factor in the hog stomach. Fox and Castle investigated Meulengracht's assumption that the observations on hog stomach are directly applicable to man by studying the anti-pernicious anemia effect of dried human fundus and dried pylorus. Their material was obtained at autopsies on adults of either sex in various age groups who had died suddenly from a heart or brain lesion and had shown no clinical or postmortem signs of infection. The stomachs were removed usually within 12 hours after death, always within 24 hours. Immediately after their removal the stomachs were opened and divided into various portions according to a schematic drawing pre-

sented by Meulengracht and Sjøberg-Ohlsen,⁸ based on the findings in the hog stomach (Fig. 1). Fox and Castle pointed out that because of the different distribution of pyloric and fundal glands in the human stomach (Paschakis and Orator¹⁰) the "pylorus" preparations employed were not pure but contained an admixture of fundal gland tissue.

pernicious anemia activity of the stomach preparation defines the site of secretion of the intrinsic factor, the conclusion will be that in man the fundal portion, not the pyloric portion, of the stomach is the most important site of intrinsic factor production. This is in keeping with the site of the degenerative processes in the stomach in pernicious anemia.

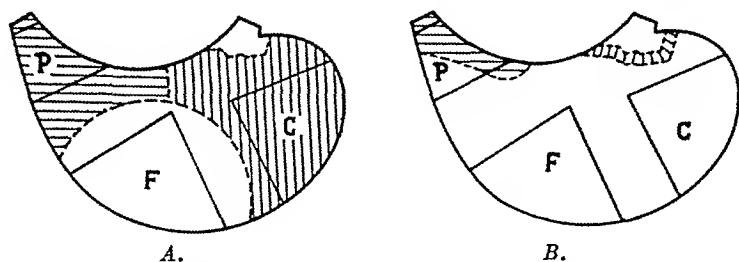


FIG. 1.—A, Distribution of pyloric, cardiac and fundal types of glands in hog stomach according to Meulengracht and Sjøberg-Ohlsen.⁸ B, Plan of incision (solid lines) employed by Fox and Castle² for pylorus, cardia and fundus preparations of human stomachs. Glandular areas according to Paschakis and Orator.¹⁰ (After Fox and Castle.)

After washing, the stomach specimens were ground together with the same amount of beef; they were then dried, powdered and defatted with ether. The therapeutic dose employed was 10 gm. of this powder 3 times daily for 10 days. The fundus preparation showed a maximal anti-pernicious anemia effect in 2 cases. One patient with an initial red blood count of 1.62 million per c.mm. treated with the "pylorus" preparation showed only a slight reticulocyte response (6.4% on the 10th day), and subsequent treatment with Ventriculin (N. N. R.) in the same dosage gave a strong second reticulocyte response.

From these findings Fox and Castle concluded that the anti-pernicious anemia activity of dried preparations from human stomach showed a distribution of activity quite different from that observed in hog stomach preparations. The fundus preparations gave a pronounced effect, whereas the pylorus preparation had only slight activity, which might be attributable to the fact that the pylorus preparation contained a considerable admixture of fundal glands. If the assumption is made that the anti-

PRESENT INVESTIGATION. In a previous paper,⁵ a description of the position of the pyloric-fundal gland border in the human stomach has been given. Utilizing this mapping of the glandular zones (Fig. 2) we have been able to separate the fundal and pyloric areas anatomically and thus to employ pure fundus and pylorus preparations in the clinico-therapeutic experiments.

Method. All the stomachs used here were removed from individuals of either sex who died suddenly, in most instances from gunshot wounds, in a few cases from cardiac lesions or carbon monoxide poisoning. The ages ranged from 17 to 66 years, most subjects being under 40. The stomachs were removed within 21 hours after death, usually within a few hours. The subserous adipose tissue was removed. The stomach was opened along the greater curvature and the mucous membrane was washed briefly with running water. The stomach was then divided into the pyloric and the fundal portions as defined by the previous studies⁵ (Figs. 2 and 3). These sections were then dried, defatted and powdered. The preparations were kept, until used, in paraffined boxes each containing 5 gm. None of the



FIG. 2.—Pyloric-fundal border in human stomach according to Landboe-Christensen.⁶ Stomach (♂ 23 years) cleared in acetic acid and transilluminated. The pyloric area represents 11% of the total stomach area.

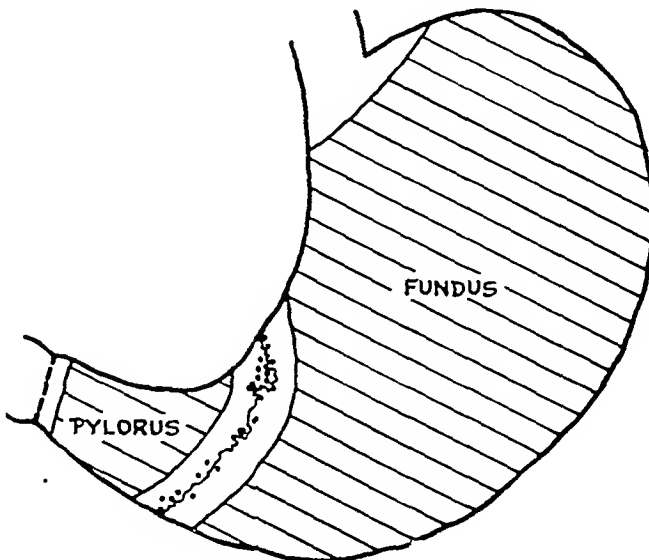


FIG. 3.—Position of pyloric-fundal gland border in the human stomach. The shaded areas indicate the pyloric and fundal portions used in the experiments.

preparations were found to contain bacteria pathogenic to man.

Case Reports. Case 1 was treated with a pure human fundus preparation and Case 2 with a pure human pylorus preparation.

CASE 1. No. 261/1946. The patient was a 38 year old woman, admitted to Medical Department A of the Rigshospital, Copenhagen, on Jan. 22, 1946, with typical pernicious anemia. Apart from a period of 2 months, 5 years before, when presumably she was given liver preparation, the patient had not been treated.

The patient was given *powdered human fundus*, 20 gm. daily for 2 days, and 10 gm. daily for the following 6 days, a total of 100 gm. The preparation was given with lunch and dinner. The patient was given the ordinary hospital diet. In addition, meat was included in each dinner. Liver was avoided. The reticulocytes began to rise on the 4th day and reached a peak of 23.9% on the 7th day (Fig. 4). During the following 5 days the reticulocyte count fell to 4%. During the next 14 days the patient was given "Pylorin" (Medicinalco), *i. e.*, pow-

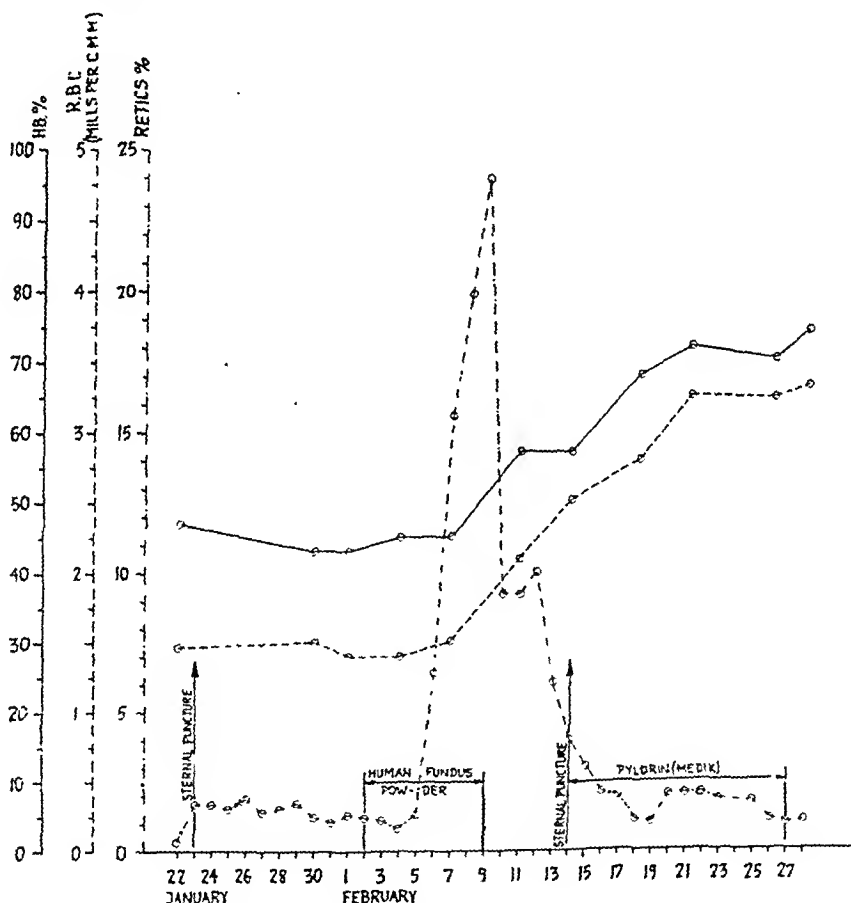


FIG. 4.—Hematologic findings. Case 1.

On admission, the hemoglobin was 47%; 10 days later it was 43%. The red blood counts were 1.46 and 1.40 millions per cmm. respectively. Gastric analysis showed histamine-fast achlorhydria. The icterus index was 5 and the serum iron was 0.221 mg. per 100 cc. Sternal puncture showed megaloblastic erythropoiesis.

dered hog pylorus, in the same dosage. This did not produce a second reticulocyte response.

The hemoglobin percentage rose in 11 days from 45 to 68%, and the red blood count from 1.4 to 2.7 millions. At the same time the sternal puncture showed a distinct change from a megaloblastic to a normoblastic bone

marrow. Serum iron on the 13th day after the start of treatment was 0.118 mg. per 100 cc.

CASE 2. The patient, a woman aged 43, was admitted on Aug. 24, 1946, to the Kommune Hospital Medical Department VII, Copenhagen, with untreated pernicious anemia.

subsequent moderate rise in the red cells and hemoglobin. The effect observed, however, was smaller than in the first case. During 18 days the erythrocytes rose from 1.3 to 1.9 millions per c.mm. and the hemoglobin from 39 to 48%. Subsequent treatment with human fundus powder and with hog pylorus powder caused second and third

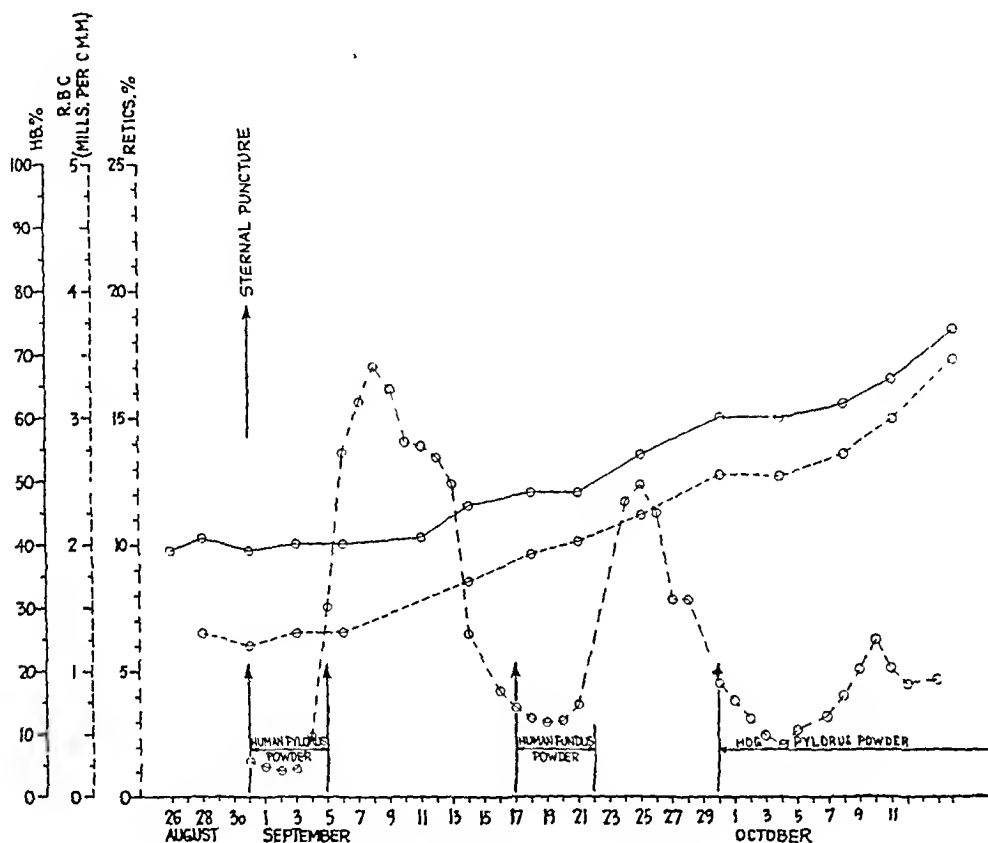


FIG. 5.—Hematologic findings. Case 2.

On admission, the hemoglobin was 41%, the red blood count 1.3 millions per c.mm., the color index 1.5. Gastric analysis with histamine showed no free hydrochloric acid. The icterus index was 37. Roentgen ray of the gall bladder showed 4 small stones. Liver function tests were normal. The sternal puncture showed megaloblastic erythropoiesis.

The patient was given powdered human pylorus, 20 gm. daily for 2 days and 10 gm. daily for the next 4 days, a total of 80 gm. Owing to the extreme difficulty in obtaining the material, only this quantity was available. The diet was the same as in the first case. Reticulocyte rise commenced on the 4th day, and the peak value of 17% was reached on the 8th day (Fig. 5), with

reticulocyte responses with peaks of 12.3% and 6.3% respectively. The sternal marrow immediately after the course of treatment with pylorus powder showed considerable normoblastic proliferation. The subsequent punctures showed the marrow obviously altered further by the therapy, but even after treatment with human fundus powder erythropoiesis was still not quite normal, particularly as indicated by the number of basophilic erythroblasts.

Comment. The feeding of 100 gm. of dried powdered and defatted stomach wall from the anatomic fundal part of the human stomach to a patient with pernicious anemia over a period of 8 days produced a striking therapeutic effect. This

demonstration of high anti-pernicious anemia activity of human fundus powder agrees with the observations of Fox and Castle and corresponds with the localization of the pathologic changes in the stomach of patients with pernicious anemia. The effectiveness of human fundus powder is in contrast, however, to the total ineffectiveness of hog fundus.

The feeding of 80 gm. of dried powdered and defatted stomach wall from the anatomic pyloric part of the human stomach to a second patient with pernicious anemia over a period of 6 days produced a moderate therapeutic effect, the reticulocytes rising to 17% on the 9th day with subsequent rise in the red cells and hemoglobin. The effect observed was smaller than in the case treated with fundus powder. Subsequent feeding of human fundus powder caused a second reticulocyte response (peak of 12.3%). Because therapy was not continuous, however, this second reticulocyte reaction, although it suggests the submaximal effectiveness of the pylorus powder in the dose given, does not prove conclusively the greater potency of fundus powder.⁹ Fox and Castle likewise observed a relative slight effect from the administration of their so-called "pylorus" preparation which they considered possibly to be the result of the presence of some glandular material of the fundal type. However, in the present experiment no glands of the fundal type were present and yet the material had definite anti-pernicious anemia activity.

The criticism could be made that secretion from the fundus of the stomach might have contaminated the preparation from the pylorus, which forms only about 11% of the total stomach area.⁵ Fox and Castle,² in their study of the distribution of the anti-pernicious anemia activity in the hog stomach, demonstrated that hog fundus was therapeutically ineffective, even when taken from stomachs allowed to remain unopened for 24 hours and consequently potentially exposed to contamination with pyloric secretions. This control observation suggests that anti-pernicious anemia activity occurs not only in association with human fundal glands, as shown previously by Fox and Castle, but also as in the present experiments in association with human pyloric glands. With the amounts of material available, it was not possible to perform an experiment in such a way as to give information as to whether fundus or pylorus powder is more active.

Summary. Dried powdered preparations were made of the fundal and pyloric parts of the wall of the human stomach. Separation was effected according to the mapping out of the pyloric-fundal gland border described previously (Landboe-Christensen). Clinical tests of the therapeutic efficiency of the preparations were carried out in 2 cases of pernicious anemia. In the doses used fundus powder gave maximal response, and pylorus powder showed moderate activity.

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RECTAL POLYPS: DIAGNOSIS, 5 YEAR FOLLOW-UP, AND RELATION TO CARCINOMA OF THE RECTUM

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THERE has been considerable controversy concerning the potential malignancy of benign rectal polyps. Bockus¹ published a review of other sources which showed a variation of from 5 to 85% in the malignancy index of rectal polyps. He believed that the wide variation was the result of individual interpretation of the observed pathologic changes. Fitzgibbon and Rankin,⁶ noting the similarity of site of origin of cancer and polyps in the gastro-intestinal tract, suggested the possibility that cancer of the rectum arose from benign polyps. Brust² reported a sex ratio in polyps of 3 males to 2 females, corresponding to the ratio in carcinoma of the rectum. Swinton and Warren¹¹ contended that in 827 cases of carcinoma of the colon and rectum, 14% could be demonstrated histologically to have arisen from benign rectal polyps. Lockhart-Mummery and Dukes⁸ reported that practically all cases of heredofamilial type of disseminated polyposis develop carcinoma of the colon, and die 20 years earlier than other cases of carcinoma of the colon. Sawyer¹⁰ contended that all polyps in the rectum are potentially malignant and that the probability of cancer increases with the number of polyps present, approaching 100% in disseminated polyposis. Buie and Brust⁴ believed that most, if not all, rectal adenomas will ultimately become cancer if not removed.

Contrary to the above evidence and opinions, Fitzgibbon and Rankin⁶ stated that some polyps never become malignant. David⁵ observed that it is an extremely

rare clinical experience to observe an apparently benign adenoma or papilloma of the rectum become malignant, even over a considerable period of observation. Lawrence⁷ in 7000 consecutive autopsies found an incidence of polyps in the rectum and colon of 3.37%. All suspicious polyps were examined microscopically and only 6.5% were found to be malignant. In only 12% of the cases having carcinoma of the colon were benign rectal polyps also present. Martin⁹ found that the size of a polyp had no bearing on the question of whether a polypoid lesion is benign or malignant. Buie³ noted that adenomatous polyps associated with malignant changes are of uniformly low-grade malignancy: usually of Grade I or II, very rarely of Grade III.

Because of the above conflicting opinions as to whether benign rectal polyps become malignant or not, we have undertaken this study of 235 cases of rectal polyps, some of which were removed and some of which were not. A 5 year follow-up study was conducted to determine whether patients who did not have their polyps removed developed carcinoma of the rectum more frequently than patients who did have their polyps removed.

Method. In this study all cases of rectal polyps found at the Henry Ford Hospital from 1930 to 1941 were included. Carcinomas of the rectum were not included as they are outside the scope of this paper. An effort was made to obtain 5 year follow-up observations on all other cases.

The number of proctoscopic examinations

* Now in practice in Oklahoma City.

required to discover the 235 cases of rectal polyps studied is not known, as no record was kept in the earlier years as to the number of proctoscopic examination done. This figure can only be estimated on the incidence of polyps found in the past 4 years. During this period they were found in 2.3% of the patients examined. On this basis we estimate that about 10,200 proctoscopic examinations were made in establishing this series of 235 rectal polyps.

Patients have been advised routinely to have rectal polyps removed. However, a number of patients did not do so. This gives us 2 groups to compare in our 5 year follow-up, namely, those who had their polyps removed and those who did not.

In this study, all polyps classified as benign were done so on the basis of microscopic examination after removal of the polyp.

The polyps were removed by fulguration after biopsy, with the exception of 3 cases. In 1 case, Roentgen ray therapy was used with subsequent bowel resection, as the polyp was in the sigmoid. In the other 2 cases, resection of the bowel was done because the polyps were in the sigmoid colon.

Results. 1. CLINICAL DATA. (a) Incidence of Rectal Polyps. The incidence of 2.3% of rectal polyps in routine proctoscopic examinations in this clinic is somewhat low compared with the literature. However, proctoscopic examination is a routine procedure for all patients in the Gastro-intestinal Division of Henry Ford Hospital.

TABLE 1.—AGE AND SEX DISTRIBUTION IN CASES OF RECTAL POLYPS

Age (yrs.)	Female	Male	Total
0-9	0	1	1
10-19	3	1	4
20-29	8	6	14
30-39	14	18	32
40-49	22	51	73
50-59	17	43	60
60-69	17	21	38
70-79	3	10	13
80 and over	0	0	0
Totals	84	151	235

In Table 1 are presented the age and sex distribution of our patients with rectal polyps, 72% occurring in the 4th, 5th and 6th decades; 65% were males. Both of these figures agree approximately with the

age and sex incidence of carcinoma of the rectum, as has been reported by Brust.²

(b) *Symptoms.* There is no evidence that rectal polyps cause symptoms, except for the occasional cases with ulceration of the polyp and possible bleeding. Table 2, dealing with symptoms, shows the predominating symptom occurring in these cases to be irritable colon distress. This is understandable, as the majority of the patients routinely proctoscoped came to the clinic because of this distress. Only 21 patients complained of rectal bleeding and only 9 patients complained of any rectal discomfort. We doubt that the rectal polyp caused all the cases of bleeding, and certainly doubt that the rectal polyp caused the rectal discomfort. However, if one assumed that the complaints in all of these 30 cases with either rectal bleeding or discomfort were due to the rectal polyp, only 12.8% of the rectal polyps produced symptoms, since there were 205 patients (87.2%) who did not have these or any other symptoms possibly related to the polyp. Obviously, the diagnosis of rectal polyp, tentative diagnosis, or even suspicion of a rectal polyp cannot be based on the symptoms that the patient presents.

TABLE 2.—SYMPTOMS IN PATIENTS WITH RECTAL POLYPS*

	No. patients
Irritable colon	132
Constipation	76
Rectal bleeding	21
Diarrhea	17
Rectal discomfort	9
Alternating diarrhea and constipation	3

* Symptoms not related to the lower gastrointestinal tract were not included.

(c) *Associated Abdominal and Rectal Lesions.* In Table 3 the accompanying abdominal lesions in cases with rectal polyps is tabulated. An analysis of these data convinces one that there is no significant association of other abdominal lesion with rectal polyps. It should be noted that only 4 of these patients had ulcerative colitis, only 3 had amebiasis, 6 had other intestinal parasites, and 10 had

benign ulcerative proctitis. There is no evidence that a causal relationship exists between any of the associated abdominal conditions and rectal polyps.

TABLE 3.—ABDOMINAL AND RECTAL LESIONS IN 235 PATIENTS WITH RECTAL POLYPS

Lesion	No.
Peptic ulcer	20
Diverticulosis	19
Cholelithiasis	12
Hemorrhoids	11
Benign ulcerative proctitis	10
Intestinal parasites	6
Ulcerative colitis	4
Amebiasis	3
Cholecystitis	3
Gastritis	3
Fistula-in-ano	2
Appendicitis	2
Congenital polyposis	2
Fibroids, acute hepatitis, gastric carcinoma, gastric polyp, malnutrition, hepatic cyst, typhoid fever	1 ea.

2. LABORATORY EXAMINATIONS AND ROENTGEN RAY FINDINGS. (a) *Stool Examinations.* Stool examinations are reported in Table 4. In 186 examinations for occult blood only 62 were positive. We cannot say that the stools that were positive for occult blood were so because of the rectal polyp. The positive tests may have been due to an excess of meat in the diet, bleeding gums, peptic ulcer, hemorrhoids, or to other conditions causing occult blood in the stool.

TABLE 4.—OCCULT BLOOD IN THE STOOL

Negative examinations	124
Positive examinations	62
1+	28
2+	17
3+	7
4+	10

(b) *Hemoglobin Determinations.* Table 5 presents the hemoglobin determinations in 218 patients with rectal polyps. Of this number only 35 had a hemoglobin less than 12 gm. Analyses of these 35 cases showed the anemia to be associated with other conditions in 21 cases. In only 14 of the 218 cases could the anemia possibly have been due to the rectal polyp. From these data, it is obvious that anemia is not usually a finding in patients with rectal polyps.

TABLE 5.—HEMOGLOBIN IN PATIENTS WITH RECTAL POLYPS*

	No.
Hemoglobin determination	218
Hemoglobin less than 12 gm.	35
Anemia associated with other condition	21
Anemia associated with polyp (benign) (anemia not explained)	7
Anemia associated with polyp (malignant)	4

* White blood count was normal except when elevated due to other conditions.

(c) *Barium Enema Examinations.* In Table 6 the results of Roentgen ray examinations of the colon in patients with rectal polyps are presented. It will be seen that an associated lesion is quite infrequent. With 179 ordinary enema examinations, colonic polyps above the rectum were found in only 5 cases. With 43 double contrast enema examinations, other polyps were found in 12 cases. This clearly demonstrates the value of a double contrast barium enema examination in the diagnosis of colonic polyps by Roentgen ray. It shows the necessity of a double contrast barium enema in every patient with a rectal polyp.

TABLE 6.—ROENTGEN FINDINGS IN PATIENTS WITH RECTAL POLYPS

	Regular barium enema	Double contrast
Total number done	179	43
Negative	115	31
Spastic colon	47	
Diverticuli	14	
Polyps (colonic)	5	12
Non-rotation of cecum	2	
Ulcerative colitis	2	
Examinations not done	56	192

3. PATHOLOGY OF RECTAL POLYPS. Of 235 patients in our series, 167 had their polyps removed, 68 failing to do so. In 32 patients multiple polyps were demonstrated, and 14 patients had recurrent polyps. The 167 patients had 175 polyps removed, 8 patients having more than 1 polyp.

(a) *Gross Pathology.* In Table 7 the gross appearance of the polyp is tabulated. It is apparent from a comparison of the general appearance of the benign and malignant polyps that there is no apparent difference. It cannot be assumed that a

polyp is benign, because it is small, pea-sized or sessile. The only way that one may determine whether any particular polyp is benign or malignant is by the histologic report. This is in agreement with the findings of Martin.⁹

In this connection, however, there is one point of some importance. Only 5% of the 273 benign polyps were ulcerated, whereas 37.5% of the 16 malignant were ulcerated. Although ulceration of a polyp is not diagnostic of malignancy, ulceration occurred over 7 times as frequently in the malignant group of polyps as in the same number of benign polyps. (The greater total number of ulcerated *benign* polyps found (see Table 8), as compared with the total number of ulcerated malignant polyps, is obviously due to the fact that, in the total group, there were 17 times as many benign polyps as there were malignant polyps).

TABLE 7.—GROSS APPEARANCE OF RECTAL POLYPS

Appearance	Benign	Malignant
Small, pea-sized . . .	84	1
Pedunculated . . .	68	8
Sessile . . .	56	5
Not stated . . .	65	2
Total polyps . . .	273	16
Ulcerated . . .	14 (5%)	6 (37.5%)

* This totals more than 235, because some patients had multiple polyps and some had recurrent polyps.

(b) *Microscopic Pathology.* In Table 8 the microscopic findings in the rectal polyps is presented. Of the 175 biopsies, 36 showed some suggestion of malignancy on the microscopic examination, although they could not be classed as malignant. It must be remembered that an adenoma frequently is growing and proliferating; hence one would expect to see some evidence of that growth in the cells present. We do not believe that the presence of one or more signs of malignancy, without invasion of the basement membrane, indicates necessarily that the polyp will become malignant. It also is to be noted that in the 16 cases of definite malignant adenomas, none of them were greater than

Grade II in malignancy. This is in agreement with Buie³ who found that adenomatous polyps associated with malignant changes have a uniformly low grade of malignancy.

TABLE 8.—MICROSCOPIC FINDINGS IN RECTAL POLYPS

Classification	No.
Benign	123
Benign but with signs of malignancy	36
Mitotic figures	19
Hyperchromatic nuclei	14
Piling up of epithelium	19
One sign	21
Two signs	14
Three signs	1
Malignant	16
Grade 1	10
Grade 2	5
Unclassified	1
Total biopsies	175

4. FOLLOW-UP STUDY OF PATIENTS WITH RECTAL POLYPS. (a) *Five to 11 Year Follow-up.* Table 9 presents the number of cases we were able to follow for from 5 to 11 years. The minimal length of follow-up included in the table was 5 years. Ten patients with benign polyps could not be followed for 5 years, because they died of other causes before the end of the 5 year period. Of the 159 patients with benign polyps, we were able to follow 117 (74%) for 5 years. Of the 68 patients who did not have their polyps removed, we were able to follow 43 (63%) for 5 years.

TABLE 9.—FIVE YEAR FOLLOW-UP OF PATIENTS WITH RECTAL POLYPS

	No.
5 to 11 year follow-up	174
Benign	117*
Not removed	43†
Malignant	14
No follow-up	61
Benign, removed	24
Not removed	25
Benign, removed, died of other causes	10
Malignant	2
Total	235

* 74%.

† 63%.

(b) *Five Year Incidence of Malignancy in Operated and Unoperated Polyps.* In Table 10 both the incidence of malignancy in biopsied rectal polyps and the incidence of development of malignancy of the rec-

tum in a 5 year follow-up observation of operated and unoperated groups of cases are presented. The incidence of malignancy in rectal polyps on first examination was found to be 5.9%. This incidence of malignancy is in close agreement with the autopsy series of Lawrence,⁷ in which he found 6.5% of polyps were malignant. This indicates that there is a rather low yet definite incidence of malignancy in rectal polyps.

their polyps removed (6.9%) actually should equal the 5.9% incidence of carcinoma in those removed on first examination plus the 2.5% incidence of those in this same group that developed carcinoma in the subsequent 5 years (8.4%). The 2 figures are closely parallel. This indicates that the group in which the polyps were not removed developed no more carcinoma in 5 years than the group in which the polyps were removed. This is strong evidence,

TABLE 10.—INCIDENCE OF MALIGNANCY AND 5 YEAR FOLLOW-UP OF PATIENTS WITH RECTAL POLYPS

	No. patients	%
A. Total number biopsied on first examination	167	
1. Carcinoma present on first examination	10	5.9
2. Benign polyps removed	157	8.4
(a) Total benign polyps removed, followed 5 yrs.	117	
(b) Number subsequently developed carcinoma of rectum	3	2.5
B. Total number polyps not removed, followed 5 yrs. or more	43	6.9
Number subsequently developed carcinoma of rectum	3	
C. Total number malignant polyps removed	16	
(a) Number malignant polyps removed, followed 5 yrs.	14	
(b) Number cases well 5 yrs. or more after excision	13	

In the group that had their benign polyps removed, 3 cases (2.5%) developed carcinoma of the rectum in a subsequent 5 year period, making the total early and later incidence of carcinoma in the operated group 8.4% (5.9% plus 2.5%). In the non-operated group of rectal polyps the incidence of rectal carcinoma over a corresponding period of 5 years was 6.9%. These observations obviously fail to support the theory that benign rectal polyps tend to become malignant (see Table 10). In our observation, however, in the group that did not have their polyps removed, only 6.9% of the cases subsequently developed carcinoma during the 5 year period. This incidence of malignancy is almost the same as the initial 5.9% incidence of malignancy in those polyps that were removed on first examination.

If benign rectal polyps become malignant with the passing of time, one would expect a much higher incidence of malignancy in polyps that have been present for 5 years than in those that are removed at once. Furthermore, the incidence of carcinoma in the group that did not have

as noted above, that malignant polyps are either malignant in the beginning, or else become malignant early, and that benign polyps do not become malignant with the passing of time.

It can also be seen from Table 10 that we were able to follow 14 of the 16 patients with malignant polyps for 5 years. Only 1 of these 14 patients followed died of carcinoma of the rectum in the 5 year period. This is evidence (1) of the low grade of malignancy that is usually present in rectal polyps, and (2) of the value of early removal of rectal polyps.

Summary. A review of the literature reveals a wide divergence of opinion as to the significance of rectal polyps. Reports vary from 5 to 85% incidence of malignancy in rectal polyps.

Our series includes 235 cases of rectal polyps, with a 5 year follow-up of 174 cases. The incidence of rectal polyps in routine proctoscopic examinations was estimated to be 2.3%. The age and sex distribution shows that 72% were found in the 4th, 5th and 6th decades and that 65% of the cases were males. Patients

with rectal polyps rarely have symptoms referable to the polyps. There is apparently no relation between rectal polyps and other abdominal lesions. Anemia, when present, is usually associated with other conditions. Stool examinations are occasionally positive for occult blood, but this finding is usually associated with some other intestinal condition.

Since 2.3% of the patients presenting themselves to the Gastro-intestinal Division for treatment had rectal polyps, and since there is no other way to diagnose a rectal polyp than by proctoscopic examination, the gastro-intestinal examination of any patient is incomplete without a proctoscopic examination.

Additional colonic polyps were found in 5 patients out of 179 by routine barium enema examinations. However, in 43 patients in which double contrast barium enema examinations were done, additional colonic polyps were found in 12 cases. This emphasizes the importance of barium enema study, and particularly of double contrast examinations in patients with rectal polyps.

There is no relationship of the size and shape of the rectal polyp to its tendency to be malignant. Ulceration, however, occurred 7 times as frequently in malignant polyps as in a similar number of benign polyps.

There were 17 times as many benign polyps as malignant polyps in the total series. Of the 16 malignant polyps that were found, none had a malignancy higher than Grade II. This indicates the low grade of malignancy in malignant rectal adenomata. Of the 16 cases of malignant polyps which could be followed for 5 years, 13 were well at that time. This also indicates the rather low grade of malignancy usually present in rectal adenomata.

The incidence of carcinoma on first examination by biopsy after removal was 5.9%. Of this group that had their polyps removed, an additional 2.5% developed carcinoma of the rectum within 5 years. This means that 8.4% of the patients who had their rectal polyps

promptly removed exhibited rectal malignancy within a 5 year period. The group that did not have the polyps removed had an incidence of malignancy over a corresponding 5 year period of 6.9%. The fact that this latter percentage is a little lower than 8.4% is almost certainly not significant but due rather to the fact the latter percentage was obtained from a smaller series of cases. This would indicate that malignant rectal polyps are either malignant in the beginning or tend to become malignant early. There is no evidence in this study that malignancy tends to develop in benign rectal polyps after some length of time.

It is common knowledge that a certain number of patients die from malignant rectal polyps. The only question is, are these polyps malignant from the beginning in most instances at least, or do they tend to become malignant with the passage of time? The same division of opinion relative to malignant gastric ulcer has existed for many years.

Conclusions. 1. Rectal polyps rarely present symptoms suggestive of their presence. Only 12% of our patients had symptoms that could possibly be related to the rectal polyp and in most of these cases these symptoms were apparently due to other causes.

2. Examination of a patient is incomplete without a proctoscopic examination.

3. Patients with rectal polyps should have a double contrast barium enema study to rule out polyps higher in the colon.

4. One cannot be guided by the size, shape or general appearance of a rectal polyp as to whether it is malignant or benign. There is a much higher percentage of ulceration in malignant polyps than in benign polyps.

5. All rectal polyps should be removed promptly, because only by biopsy can one determine if they are malignant or benign, and only in this way can the patients be given the maximum chance of a permanent cure, and without major surgery.

6. Rectal polyps, when malignant, are usually of a low grade of malignancy.

7. The biopsy incidence of malignancy on first examination in the rectal polyps in this series was 5.9%.

8. The total incidence of malignancy for the 5 year period is not significantly different in the group that had their polyps removed (8.4%) than in the group that did not have their polyps removed (6.9%).

9. The observations noted above strong-

ly suggest that malignancy usually either develops very early in rectal polyps or is present from the start. There is no evidence available from this study that benign adenomata of the rectum become malignant with the passage of time.

10. The prompt removal of the majority of rectal polyps in this group of cases resulted in a 5 year cure without any major surgery in 13 of 14 patients with malignant rectal polyps.

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ATTEMPTS TO INHIBIT RH ANTIBODY PRODUCTION IN RABBITS

USE OF ETHYLENE DISULPHONATE, SODIUM SALICYLATE, PYRIBENZAMINE, AND A AND B SPECIFIC BLOOD SUBSTANCES

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UNTIL recently, erythroblastosis fetalis had been treated principally postpartum. The association of the presence of Rh antibodies in the maternal blood with the occurrence of erythroblastosis fetalis has led to attempts to abolish the antibodies in the pregnant woman, with the hope of preventing or decreasing the severity of the disease. Theoretically, maternal circulating antibodies could be decreased or abolished by (1) inhibition of the production of antibodies, (2) neutralization of the maternal circulating antibodies by a corresponding Rh hapten, (3) prevention by some other, so far unknown, means of the antigen-antibody combination from going to completion, or (4) removal of the circulating antibodies by some mechanical means such as plasmapheresis. This latter principle is now being applied to the newborn fetus when an exsanguination transfusion is done. An approach to the first possibility has been suggested by Wiener,⁴ in which he proposes giving an antigen more potent than the Rh antigens and, thus by a competition of antigens, causing the antibody producing mechanism, whatever it may be, to produce the antibody corresponding to the antigen given instead of the Rh antibodies. Two chemotherapeutic approaches have been suggested, although it is not known by what means their proposed effectiveness in reducing circulating Rh antibodies occurs. One, as suggested by Homburger,¹ is the administration of sodium salicylate,

along with *Macacques rhesus* cells, to rabbits and guinea pigs, and so reduce the production of Rh antibodies in these animals. The other, as reported by Kariher and Miller,² is the administration of ethylene disulphonate* at weekly intervals during pregnancy, thus causing a reduction in Rh antibody levels instead of the usual continued rise up to term.

The purpose of this paper is to report our attempts to inhibit or reduce Rh antibody production in rabbits by the use of (1) ethylene disulphonate, (2) salicylates, in an attempt to duplicate Homburger's experiment, (3) A and B specific blood substances,† in accordance with Wiener's theory, and (4) Pyribenzamine‡ with the idea that histamine might be related to antibody production and, therefore, an antihistamine drug might reduce antibody production.

Procedure. Various colored healthy female rabbits were used with one exception in the ethylene disulphonate experiment where a male (Rabbit 2) was used. They were given 2 series of 3 daily intravenous injections of 1 cc. of 1:100 dilution of citrated *Macacques rhesus* blood with an interval of 4 days between the series. The rhesus blood was taken from the same monkey for all but the control experiment. Before the rhesus cell injections, and at certain intervals during the experiments, 5 cc. of blood were taken from the marginal ear veins by means of a cut with a razor blade. After centrifugation, the serum was removed and inactivated for $\frac{1}{2}$ hour at 52° to 56° C.

* The ethylene disulphonate (Allergosil Brand) was generously supplied by the Spicer-Gerhart Company, Pasadena, California, in 2 cc. sterile ampoules of a 1:10⁻¹⁵ dilution in triple distilled water.

† Blood group specific substances A and B were generously supplied by Sharp & Dohme, Philadelphia, Pennsylvania, as a sterile solution.

‡ Pyribenzamine HCl was generously provided by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey, as the dry sterile powder. This was dissolved in sterile water to make the 1% solution used.

Because most of the normal rabbits' sera contained agglutinins and conglutinins against the ORh,Rh₂M test cells, the following technique for absorption of these unwanted antibodies was used. One cc. of the inactivated serum was mixed with 5 cc. of packed ORh-M or ORh-MN red blood cells which had been washed 3 times with normal saline and packed in 15 cc. conical centrifuge tubes by centrifuging at approximately 2000 r.p.m. for 10 minutes. This serum-red blood cell mixture was allowed to stand at room temperature for 1 hour, during which it was mixed 4 to 5 times by inversion of the centrifuge tubes. The red blood cells were packed again and the absorbed serum removed. Four persons of Types ORh-M or MN* were used as sources for the absorbing red blood cells. Two were used for the control experiment. At a later date, the same 2 plus 2 others were used, each for 1 of the other 4 experiments; so that in all but the control experiment, red blood cells from the same person were used for the absorptions in any 1 experiment. It was found that 3 cc. of packed red blood cells would completely absorb the anti-O, anti-M, and probably anti-human antibodies from some of the rabbit sera, but that some sera required 4 or 5 cc. to absorb these antibodies. Therefore, 5 cc. were chosen as the most satisfactory amount, and it proved to be so in all cases except Rabbits 8, 7, and 8 in the ethylene disulphonate, A and B substances, and salicylate experiments respectively, where the conglutinin Rh antibody persisted to a slight extent after the above absorption. Since the test cells used were of Group O, it was felt that the absorption of anti-O and anti-human antibodies was essential. Anti-M antibodies were absorbed because it has been shown that rhesus cells given to rabbits may cause the production of anti-M antibodies.³

Both agglutination and conglutination techniques were used in testing for the Rh antibodies. Three drops (each drop equals approximately 0.05 cc.) of the inactivated, absorbed serum were mixed in 60 by 10 mm. tubes with 1 drop of a 2% suspension of ORh,Rh₂M red blood cells in saline or AB serum (for agglutination or conglutination respectively). The test red blood cells were always fresh and came from the same person throughout the experiments. After incuba-

tion at 42° C. for 1 hour and centrifugation at 500 r.p.m. for 1 to 2 minutes, the amount of agglutination or conglutination was measured. Red blood cell clumping, easily visible macroscopically, was graded 4+. If this was not present, a drop of the mixture was removed with a glass rod to a slide and examined microscopically under low power for decreasing degrees of clumping classified as 3+, 2+, 1+ and =, the latter being the least amount of clumping discernible microscopically.

In the case of the A and B substances experiment and the A and B substances control experiment, where the anti-A and anti-B titers were measured, the serum was inactivated and absorbed as above, except that in the A and B substances control experiment, ORh + M cells from a constant source were used. Serial dilutions of 1:2, 1:4, 1:8, etc., were then made with a pipette in 60 by 10 mm. tubes, starting with 0.1 cc. of serum and 0.1 cc. normal saline. To these saline dilutions was added 0.1 cc. of a fresh 2% saline suspension of ARh-MN or BRh-MN red blood cells each from the same source throughout the experiments. The tubes were shaken and allowed to stand at room temperature for 1 hour, after which they were centrifuged at 500 r.p.m. and read macroscopically and microscopically as in the Rh antibody tests.

Control Experiment. Nine rabbits with average weights ranging from 6½ to 9½ lbs. (average 8 lbs.) during the 64 days of the experiment were given rhesus cells as above on Days 1, 2, 3, 8, 9, 10. The occurrence of agglutinating and conglutinating antibodies was tested for on the 7th, 14th, 17th, 23rd, 29th, 38th and 64th days. The results are recorded in Figures 1 and 2.

Ethylene Disulphonate Experiment. Eight rabbits with average weights ranging from 7 to 11½ lbs. (average 8½ lbs.) during the 38 days of the experiment were given the rhesus cells on Days 1, 2, 3, 8, 9, 10. On every 3rd day from Day 1 through Day 28, and on Days 31, 32, 34, 36, 38 they were given 0.5 cc. of ethylene disulphonate (1:10⁻¹⁵ dilution in sterile triple distilled water) intramuscularly into the hamstring muscles alternating between the right and left sides. In accordance with the instructions accompanying the solution, no antiseptic was used, the shaved skin merely being wiped off with

* Rh—means red blood cells giving no agglutination with anti-Rho serum.

dry sterile cotton, and the solution was rapidly drawn into the syringe without the needle, the needle then attached, and the solution promptly injected. Serum for the 29th day test was drawn about 24 hours, and on the 38th day, about 2 to 3 hours after an ethylene disulphonate injection. Rabbits 2 and 7 were given no ethylene disulphonate after the 31st day to determine whether the Rh antibody response of these 2 would differ from that of the other 6 rabbits who were receiving ethylene disulphonate at a frequency increased over that of the first 29 days.

Salicylate Experiment. Eight rabbits, with average weights ranging from 5 $\frac{3}{4}$ to 7 $\frac{1}{4}$ lbs. (average 6 $\frac{1}{2}$ lbs.) during the 26 days of the experiment, were given rhesus cells on Days 4, 5, 6, 11, 12, 13. Then 0.5 gm. of sodium salicylate as 10 cc. of a 5% sterile aqueous solution* (slightly more than 0.16 gm./kg.) was given subcutaneously daily from Day 1 through Day 18 (48 hours before the first sera for Rh antibody testing was obtained). This plan was adopted in an attempt to duplicate the conditions of a similar experiment reported by Homburger.¹ Daily injections were then given from Days 20 to 26. Serum

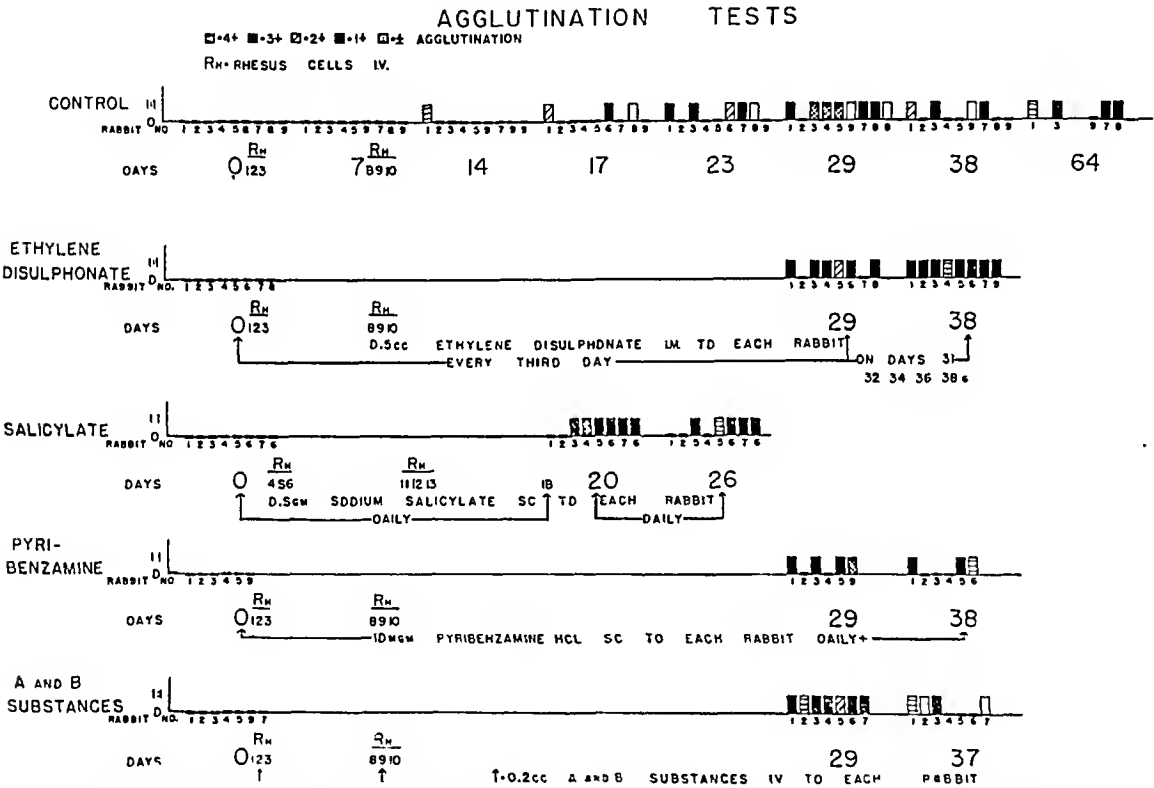


FIG. 1.—* During this period, ethylene disulphonate was given to all except Rabbits 2 and 7.
+ Pyribenzamine HCl was omitted on the 34th day; otherwise the injections were daily.

Pyribenzamine Experiment. Six rabbits, with average weights ranging from 6 $\frac{3}{8}$ to 8 $\frac{1}{4}$ lbs. (average 7 $\frac{1}{2}$ lbs.) during the 38 days of the experiment, were given the rhesus cells on Days 1, 2, 3, 8, 9, 10. Daily, except for the 34th day, they were given 10 mg. (approximately 3 mg./kg.) of Pyribenzamine HCl as 1 cc. of a 1% sterile aqueous solution subcutaneously. Serum for testing was taken approximately 24 hours after a Pyribenzamine injection.

salicylate levels were taken on Day 18, approximately 20 hours after the previous sodium salicylate injection, and on Day 22, approximately 1 to 2 hours after the previous sodium salicylate injection.

A and B Specific Blood Substances Experiment. Seven rabbits, with average weights ranging from 6 to 8 $\frac{1}{2}$ lbs. (average 7 lbs.) during the 37 days of the experiment, were given rhesus cells on Days 1, 2, 3, 8, 9, 10. On Days 2 and 9 they were given 0.2 cc. of A and B

* Eli Lilly and Co.

specific substances intravenously. Serum samples on Days 0, 29 and 37, were tested for Rh, anti-A and anti-B antibodies.

A and B Specific Blood Substances Control Experiment. Three rabbits, with average weights ranging from 6 to 7½ lbs. (average 7½ lbs.) during the 15 days of the experiment were given 0.2 cc. A and B specific substances intravenously on Days 1 and 7. Serum was drawn on Days 0, 7 (before the A and B substances injection on that day), 11 and 15. It was inactivated, absorbed and titered as explained above.

38th day. This was done in order to determine whether the substances under study would hasten or delay the peak of antibody response.

It appears from these results that none of the tested substances appreciably reduce or inhibit Rh antibody production. There are, in fact, higher incidences of Rh antibody occurrence in the ethylene disulphonate experiment on the 38th day, and, in the salicylate experiment, on the

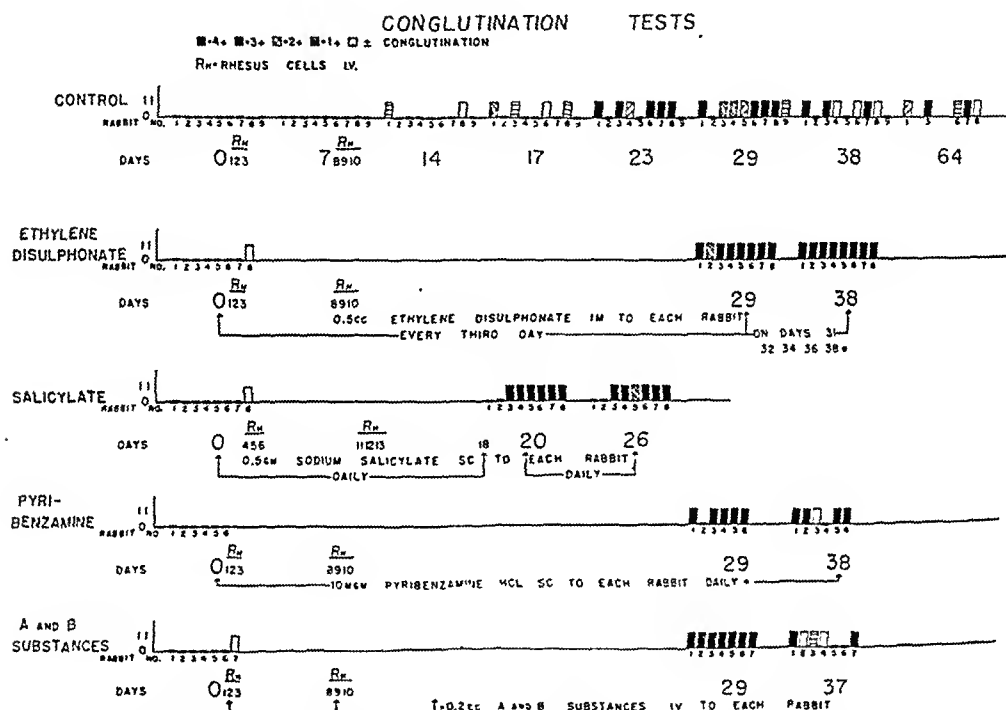


FIG. 2.—* During this period, ethylene disulphonate was given to all except Rabbits 2 and 7. + Pyribenzamine HCl was omitted on the 34th day; otherwise the injections were daily.

Discussion. The experiments show that following the injection of *Macaca rhesus* cells, both agglutinating and conglutinating Rh antibodies are formed in from 66 to 100% (average 85%) of the rabbits. In the control experiment, the highest incidence of the occurrence of Rh antibodies seems to be around the 29th day after the first rhesus cell injection, and it is for this reason that this day was chosen in the other experiments to test for Rh antibodies. In addition, in these experiments, the sera were tested on the

17th day than in the control experiment. These differences might be due to the fact that a different monkey's blood was used in the control experiment than in the ethylene disulphonate and salicylate experiments.

The failure of these substances, as used in these experiments, to reduce or inhibit Rh antibody production in rabbits does not necessarily mean that they will not be effective in humans. In fact, ethylene disulphonate seems to have had an effect in the 3 pregnancy cases reported by

Kariher and Miller,² although it is made clear that those cases are only a preliminary report. Although we have attempted to duplicate the experimental conditions of Homburger's¹ work, our results indicate no inhibition or reduction of Rh antibody production by sodium salicylate and so are contradictory to his results. It can only be said that Pyriben-

the 2nd injection, on the 7th day, there seems to be no further rise, at least during the next 8 days. These 15th day anti-A titers of the control rabbits seem to be about the same as the 29th and 37th day titers of the rabbits which had also been given the Rh antigen. It is concluded, therefore, that the rabbits given rhesus cells, in addition to the A and B sub-

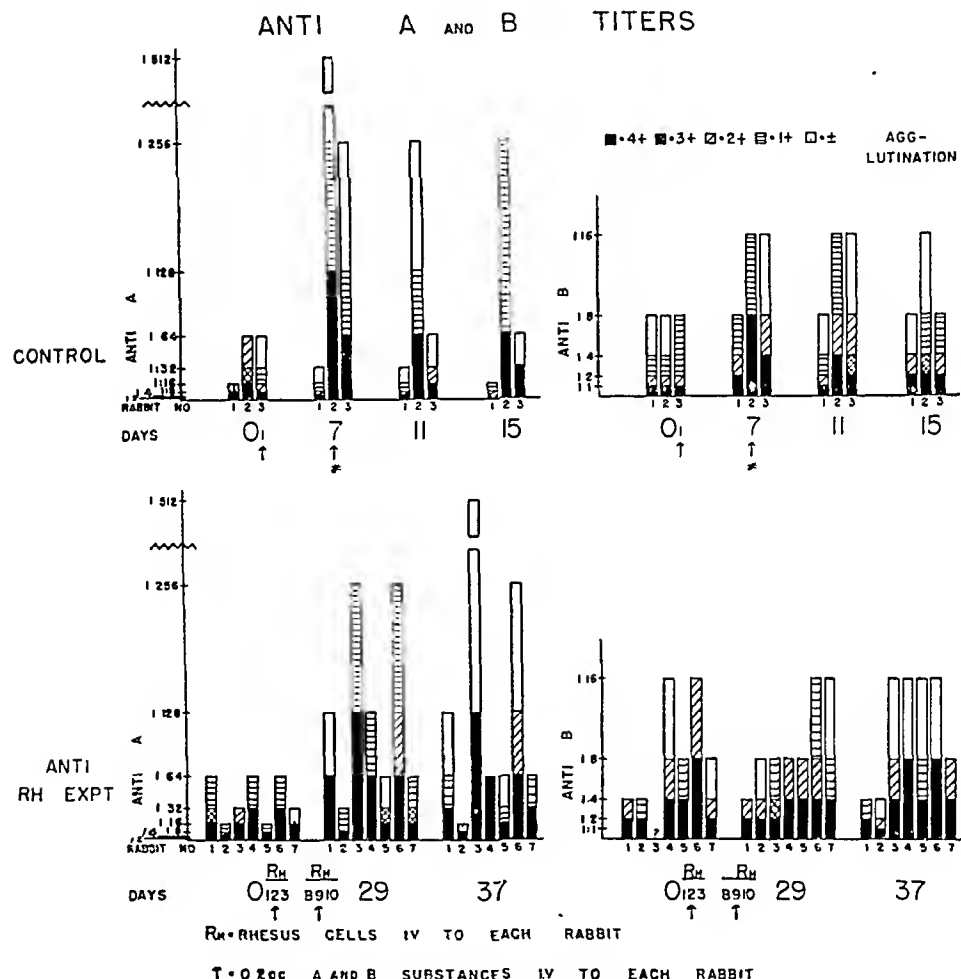


FIG. 3.— On this day the A and B specific substances were given after the sera for the titers were taken. ? Insufficient sera for this titer.

zamine exerts no inhibitory effect on Rh antibody production in rabbits, under the conditions of this experiment. It has in the past been reported to have no effect in reducing precipitin titers *in vitro* or complement titers *in vivo*.

From Figure 3 it can be seen that after 1 injection of 0.2 cc. A and B substances intravenously, the anti-A titers of the control rabbits rose by the 7th day. After

stances, produced a rise in their anti-A titers, and that that rise is approximately the same as that occurring in control rabbits given only A and B substances. It is worthy to note that there was not only a significant rise in the total anti-A titers but also in the amount of 4+ agglutination. In neither the control nor experimental rabbits was there any appreciable rise in anti-B titers.

Assuming that the human blood Group A antigen in the A and B specific substances is a potent antigen, and that it is a more potent one than the Rh antigen on the rhesus cells, the appearance of Rh antibodies in these rabbits, similar to those of the Rh control rabbits, would not seem to lend support to Wiener's theory of competition of antigens.⁴ In 1 case mentioned by Kariher and Miller,² administration of A and B specific substances at weekly intervals during the last 6 months of pregnancy had no effect on the course of Rh antibody production, with the result that an infant was born which died of hemolytic disease of the newborn.

Sera from 2 of the Pyribenzamine rabbits (No. 1 and 6) were tested with OR_hM cells and found to give identical agglutination as with OR_hRh₂M test cells. Due to the rarity of rh' and rh" cells, we were unable to test the sera for anti-rh' and anti-rh" antibodies. From this, it can only be concluded that these rabbits produce at least anti-Rh₀ antibodies.

Many of the sera were titrated using saline and AB serum dilutions of the rab-

bit sera for agglutinating and conglutinating titers respectively. It was found that, with but 2 exceptions, all of the sera did not titer past the 1:1 dilution using the agglutination technique. Two sera titrated to a 1:2 dilution. Using the conglutination technique, however, many of the sera titrated to 1:4 or 1:8 and one as high as 1:32.

In the salicylate experiment, no free salicyl radical was demonstrable in the sera 20 hours after an injection of sodium salicylate. However, between 1 to 2 hours after a salicylate injection, levels ranging from 36 to 44.8 mg. % were obtained in all 8 rabbits.*

Summary. 1. A method is presented for producing Rh agglutinating and conglutinating antibodies fairly consistently in rabbits.

2. Under the conditions of these experiments, no effect in reducing or inhibiting Rh antibody production in rabbits could be demonstrated by the administration of (1) ethylene disulphonate, (2) sodium salicylate, (3) Pyribenzamine HCl or (4) A and B specific blood substances.

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VARIATION IN THE PROTHROMBIN TEST TECHNIQUE

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THE recent literature places a great deal of emphasis on the many variations in performing the prothrombin test. It is quite evident that these variations in practice lead to much confusion in the interpretation of the results obtained, and in the guidance of dicoumarol (3,3'-methylenebis-4-hydroxycoumarin) therapy. The errors introduced by the use of whole blood "rapid tests" and diluted plasma have been discussed in a previous communication.³

Recently, Martin *et al.*⁴ reported the differences produced by variations in the order of mixing the reagents. One of 2 procedures is usually followed: in Quick's method,⁵ 0.1 cc. of whole plasma is mixed with 0.1 cc. of thromboplastin emulsion and then 0.1 cc. of 0.025 M CaCl₂ is added; in the Link²-Shapiro⁶ methods, the thromboplastin and calcium are premixed and the plasma is added to this mixture of reagents. Using Brambel's modification¹ of the Quick method, Martin and his co-workers found that addition of the plasma to the premixed calcium-thromboplastin solution produced shorter plasma clotting times than when plasma and thromboplastin were first mixed, and the CaCl₂ added later. Brambel's modification uses whole plasma diluted to 12.5 % with 0.9 % NaCl solution.

This variation in methods was studied in our laboratory in conjunction with other experiments on the prothrombin test.

EXPERIMENTAL WORK. A series of 10 "normal" patients, free from hepatic or cholecystic disease or blood dyscrasias, was studied. Difco thromboplastin (acetone-dehydrated rabbit brain) was used in these tests. Using whole plasma, prothrombin times were performed by the

method of Quick and by the Link modification (see above). Each plasma was diluted with 0.9 % saline solution to provide plasma concentrations of 100, 50, 40, 30, 20 and 10 %; 3 determinations, by each method, were carried out at each dilution. The 3 values were then averaged and the resulting hyperbolic curves were plotted for each plasma. A composite curve of the 30 determinations by each method is shown in Figure 1. The mean standard deviation for each dilution was calculated, and also the standard deviation of the differences of the means, using the formulæ:

$$(\text{mean standard deviation}) \sigma = \sqrt{\frac{\sum (x^2)}{N}} \quad \text{and}$$

(standard deviation of difference of the means)

$$\sigma_D = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$$

These results are indicated in Table 1.

Results. As seen in the composite curves (Fig. 1), prothrombin times with whole plasma (100 % concentration) and in dilutions to 30 % were shorter by Quick's method than by the Link modification. At plasma concentrations of 10 to 20 %, the clotting occurred more quickly by the Link method.

In each case, a peculiar effect occurred between the dilutions of 20 and 30 %; the curves crossed each other. So far, no explanation can be offered for this phenomenon. However, it is most interesting that this occurred in each plasma sample. Since both methods used diluted plasma this "crossing point," the possibility of dilution of "antiprothrombins" in either method can be excluded.

From the computation of the standard deviations (Table 1), it may be seen that

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there is a much smaller standard deviation by Quick's method than by the Link-Shapiro technique. At all points on the curves, except 1 (20%), the difference in values between the 2 procedures is greater than 3 times the standard deviation of the differences of the means. This indicates that the difference in these 2 methods is

statistically significant, since they are greater than 3 times the standard deviation of the difference of the means. The actual standard deviation at each plasma dilution is shown to be less with the method of Quick. The plasma clotting times were more rapid between 100 and 30% by Quick's method, but were more

TABLE 1.—COMPARISON OF THE STANDARD DEVIATION BY THE METHODS OF QUICK AND LINK
Standard deviation of the difference of the means

Prothrombin (%)	Quick		Link		Standard deviation of the difference of the means		
	Av. (sec.)	S.D.*	Av. (sec.)	S.D.	Diff. (sec.)	S.D.†	3 × S.D.†
10	74.2	±5.3	58.4	±9.1	15.8	±1.93	±5.79
20	37.5	±3.8	35.6	±4.4	1.9	±1.08	±3.24
30	27.1	±2.9	28.4	±4.0	1.3	±0.29	±0.87
40	22.1	±2.0	25.3	±3.6	3.2	±0.75	±2.25
50	19.0	±1.6	23.2	±2.9	4.2	±0.61	±1.83
100	14.4	±0.9	19.9	±2.9	5.5	±0.18	±0.54

* S.D. = standard deviation.

† S.D.† = standard deviation of the difference of the means.

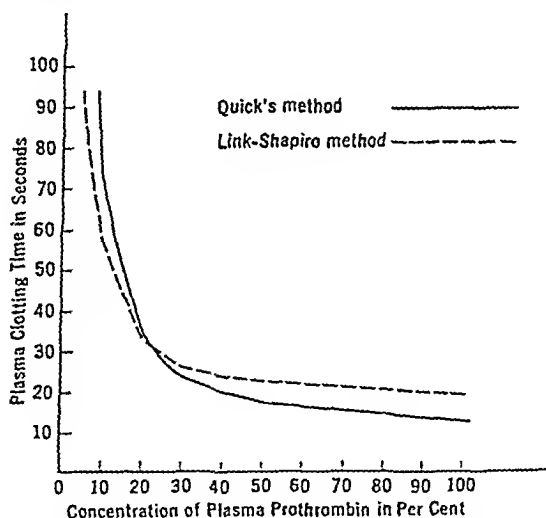


FIG. 1.—Composite curves of a study on ten patients.

statistically significant, and that one procedure cannot be substituted for the other.

Summary. Two variations in the prothrombin test technique have been discussed, and a laboratory study and comparison of these methods is presented. A statistical study of the results has been made and shows that the differences in values obtained by the two methods are

rapid between 10 and 20% by the Link modification.

As shown by the increasing standard deviation with the increased dilution of the plasma, by either method, the value of using diluted plasma (especially saline dilutions) in the prothrombin test is doubtful.

The author wishes to express his appreciation to Dr. Jules H. East, for his interest and assistance in this work.

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A STUDY OF THE MECHANISM AND TREATMENT OF EXPERIMENTAL HEAT PYREXIA*

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THE victims of excessive environmental temperature develop 1 of 3 fairly well defined clinical states: (a) heat exhaustion (heat prostration) characterized by little, if any, elevation of rectal temperature, normal or reduced skin temperature, profuse sweating, and syncopal symptoms; (b) heat cramps, characterized by painful spasms of skeletal muscles, diminished concentration of sodium and chloride in the blood,¹⁸ relieved by administration of salt water; and (c) heat pyrexia (heatstroke). It is believed that the term "heat pyrexia" (as employed by Talbott¹⁸) is more descriptive and, hence, more desirable than "heatstroke," "sunstroke," etc. In this communication the terms are used synonymously. Victims of heat pyrexia present a striking clinical picture, with marked elevation of body temperature, often as high as 110° F., prolonged coma, hot, dry, flushed skin, a bounding pulse, convulsions, petechiae, and often a fatal termination in vascular collapse, sometimes associated with pulmonary edema. Dissatisfaction with the results of treatment of this malignant disorder led to a review of available literature, and to the experimental study herein described.

REVIEW OF THE LITERATURE. From the literature, it is apparent that many fundamental facts of etiology, pathogenesis, pathologic physiology and principles of treatment are well established. It is also apparent that there are gaps in this knowledge, bridged—in lieu of controlled research—by empiricism. This information may be summarized as follows:

1. *Heat pyrexia occurs under environmental conditions which strain the heat*

dissipating mechanisms to the utmost. In the normal subject, thermostasis is achieved by a delicate balance between chemical heat production and physical heat loss. For the production of heat pyrexia, an environmental temperature exceeding body temperature—permitting heat loss only by evaporation—has been found by all observers whose reports have come to our attention. Willcox,¹⁹ Morton,¹⁶ Borden *et al.*,⁴ and others have stressed the etiologic importance of high relative humidity and high wet-bulb thermometer readings, conditions rendering heat loss by evaporation difficult. Besides such an environment, the outstanding predisposing factors are age and alcoholism. The analyses of Gauss and Meyer,⁸ and Ferris *et al.*⁶ suggest that it is acute alcoholism, *per se*, whether in the chronic alcoholic or not, which predisposes to heat pyrexia; that the chronic alcoholic is most susceptible during his debauch.

2. *In an environment which prohibits heat loss except by evaporation, heat pyrexia is induced in man by a cessation of sweating.* In an able clinical study, Ferris, Blankenhorn, Robinson and Cullen⁶ obtained a history of cessation of sweating shortly before the onset of heatstroke in 17 of 44 patients observed during 2 heat waves in 1938. Furthermore, absence of sweating was observed in all 44 patients on admission. Absence of sweating has also been reported in the analysis of Gauss and Meyer.⁸ The clinical picture, typically of a hot, dry skin, is entirely in accord with these explanations. The available evidence⁶ indicates that acidosis, circulatory failure, increase in metabolic

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rate, etc., are effects rather than causes of the hyperpyrexia.

Once sweating has ceased, the development of hyperpyrexia is inevitable. Heat loss can then occur only through insensible water loss. It has been shown by Hardy and Muschenheim,¹⁰ that as a near-perfect "black-body radiator," the body absorbs radiant heat at high external temperatures as readily as it radiates heat at lower temperatures. Cutaneous vasodilatation and increased skin flow serve to carry heat rapidly from the skin to deep tissues. As hyperpyrexia develops, as a secondary effect of heat on cellular oxidative processes, heat production increases. Thus, indeed a vicious cycle of absorption of radiant heat—increased skin flow—increased production is instituted.

3. *In heat pyrexia there is widespread, probably generalized, cellular damage of severe degree.* Damage to the cells of the central nervous system is evident in the coma and convulsions which characterize the disorder, and in the psychic disturbances of the recovery phase. Logue and Hanson¹⁴ reported electroencephalographic abnormalities of 3 months duration in a patient with heatstroke. They also described electrocardiographic evidence of myocardial injury, disappearing after 3 months. Damage to the liver cell, as evidenced by jaundice^{14,21} and prolonged prothrombin times,²¹ have been reported. The urinary findings are those of a severe febrile nephrosis. Endothelial damage, as evidenced by hemorrhages into the skin, brain, lung, gastrointestinal tract and endocardium, has often been reported, and was the subject of a special study by Wright, Reppert and Cuttino,²¹ who found that capillary bleeding antedates any demonstrable alteration in the blood-clotting mechanism. Studies of autopsy material¹¹ show morphologic evidence of generalized cellular damage.

4. *A state of acute circulatory failure regularly complicates severe cases of heat pyrexia.* Hartman¹¹ produced fatal heatstroke in dogs for study of the pathology of heatstroke. He reported that all dogs

who did not die immediately died subsequently of vascular collapse. Kopp and Solomon¹² reported 8 cases of severe shock in patients who apparently developed heatstroke in the Kettering hypertherm. Ferris *et al.*⁶ found the blood pressure at shock levels in 7 of 34 of their patients. They emphasized that shock is not important in the pathogenesis of hyperpyrexia, but their data suggest that it is a grave complication. In the case reported by Logue and Hanson¹⁴ the blood pressure was "unobtainable."

5. *The mechanism of this vascular collapse has not been established.* The available data suggest several mechanisms:

(a) The shock may be hematogenic, due to extravasation of plasma, with reduction of circulating blood volume. At skin temperatures of 42° C., capillary pressure has been measured by Landis,¹³ by capillary puncture, and found to exceed the normal by approximately 100%. Blood flow through a part is increased by elevating the temperature of the part,¹⁷ and fluid transudation is actually increased.¹³ Flinn and Scott⁷ found evidence of hemoconcentration in dogs subjected by hot environment to a degree of hyperpyrexia which was less than that required to produce heatstroke. Kopp and Solomon¹² studied the blood volume in patients who developed shock during therapeutic hyperpyrexia. By the Evans dye method, these patients in shock were all found to have reduction in blood volume of 10 to 32%. On the other hand, Talbott *et al.*,¹⁸ and Ferris *et al.*⁶ reported that serum protein and hematocrit studies indicated that hemoconcentration was either absent entirely or present to a less degree in patients with heatstroke than in patients with severe heat cramps.*

(b) The shock may be related to, or caused by, chemical changes in the blood. Flinn and Scott⁷ reported that unanesthetized dogs, whose temperature was raised to 41.5° C. by external heat, exhibited a very rapid fall in plasma CO₂ content, to about 25 to 30 volumes per 100 ml., together with alkalosis, the blood

pH rising from 7.55 to about 7.80. Hall and Wakefield⁹ found that in dogs subjected to heatstroke, the plasma CO_2 combining power fell markedly, but so did the blood pH. Associated with this acidosis there was marked accumulation of lactic acid in the blood. These differing findings are not necessarily incompatible, for in the early stages of hyperpyrexia in the dog, it is reasonable to expect an alkalosis due to hyperventilation and acapnea. In the latter stages this might be overbalanced by the accumulation of fixed acids (*e. g.*, lactic) producing acidosis. Bazett³ observed in man that hot baths, which elevated the body temperature to 40°C ., produced a lowering of alveolar CO_2 . Tetany was frequently produced. Adolph and Fulton¹ reported the production in man, by artificial fever, of a slight increase in blood pH, together with a slight decrease in blood CO_2 content. We have found no reports in man of changes in blood pH or CO_2 content comparable in magnitude to those found in the dog. This is not surprising, considering the difference in the heat dissipating mechanism of the 2 species. Ferris *et al.*⁶ found values of serum electrolytes in heatstroke patients on both sides of normal, but never grossly abnormal; blood CO_2 content was lowered, but never enough to produce coma or shock. It seems apparent that in man—unlike the dog—the chemical changes in the blood thus far observed are inconsequential in magnitude.

(c) The vascular collapse may be due to heart failure. An asphyxial form of heatstroke, with cyanosis and venous distention was described by Osler, and is mentioned in several textbooks. Pulmonary edema was said to have been a common terminal event in fatal cases reported by Wilcox.¹⁹ Ferris *et al.*, however, found pulmonary edema in only 1 of 44 patients, and no cases with markedly elevated venous pressure. Pulmonary edema has been found in dogs dying of experimental heatstroke.⁹ Wilson²⁰ reported subendocardial hemorrhages involving the left ventricle and interventricular septum in 4 cases

coming to autopsy. Borden *et al.*⁴ reported similar postmortem findings in 3 cases.

(d) The shock may be due to a generalized dilatation and atony of arterioles and capillaries. This is the familiar mechanism of the neurogenic or vasogenic type of peripheral circulatory failure, in which peripheral pooling of blood prevents adequate venous return and cardiac output. Bazett³ discussed the reasons for believing that in acute exposures to excessive heat a cutaneous vasodilatation must be compensated by a splanchnic vasoconstriction. It would seem not unlikely that the damage to which the entire central nervous system is particularly susceptible, might fail to effect this compensation. It is also possible that the splanchnic vessels dilate as a result of the direct stimulus of heat or of acid metabolites. Wright *et al.*²¹ described clinical evidence of capillary atony in their case.*

6. *Rapid reduction of hyperpyrexia is of paramount importance in therapy.* There are, however, 2 schools of thought as to the optimum method of achieving this reduction.

(a) A prevailing opinion indicates that the hyperpyrexia is most quickly and safely reduced by evaporative means. After the patient is wrapped in a wet sheet, several electric fans are played on him while his skin is massaged through the sheets, which are kept wet. Such therapy is recommended by Christian,⁵ Meakins,¹⁵ Yater,²² and Barr.² This therapy is said to be preferable to the ice-bath, because: (1) the evaporation of 1 gm. of water removed 7 times as much heat as the melting of 1 gm. of ice, and (2) the ice-bath is said¹⁵ to cause cutaneous vasoconstriction, and thereby actually to interfere with heat loss. The ice-bath is also said²¹ to place the patient in danger of "collapse." We are aware of no experimental evidence, and no controlled clinical studies, to support either of these objections to the ice-water bath.

(b) Cooling of patients by ice-water bath was found efficacious by Ferris *et al.*⁶

in reducing the hyperpyrexia in 25 patients with severe heatstroke. It was possible to effect a reduction to 102° F., or below, in from 9 to 40 minutes in all cases. Untoward effects were observed in 1 patient, cooled to 99° F. before removal from the ice-water, in that the temperature subsequently fell to 96° F. and the patient then developed vascular collapse and died. In their other patients the ice-water bath did not produce shock or skin pallor. On the contrary, the effect on consciousness and blood pressure was salutary. The temperature of 8 mildly ill patients (conscious, temperature not over 106° F.) was reduced by sheets and fans, but by contrast hyperpyrexia of 2 severely ill patients could not be reduced by this method. Gauss and Meyer⁸ also reported prompt reduction of hyperpyrexia by ice-tubbing, with a tendency toward excessive cooling, and the production of subnormal temperatures. The iced-water tub bath was recommended by Talbot¹⁸ for severe heat pyrexia.

From this review of the literature it would seem apparent that there are at least 3 important unsolved problems relative to heatstroke:

1. What are the mechanisms of the circulatory collapse which complicates stroke? Is it cardiac or peripheral? Obviously, rational treatment must depend upon an understanding of the type of failure present.

2. What is the most effective means of reducing the hyperpyrexia?

3. Why do the patients stop sweating?

Since it is difficult or impossible to study these questions under controlled conditions in man, animals have been utilized in the present study, in an attempt to answer the first 2 of these questions. Since the commonly available laboratory animals do not have a sweating mechanism comparable to that of man, no attempt has been made to answer the third question.

Experimental Studies. Heat pyrexia was produced in dogs, rats and mice by placing them in a box heated by electric light bulbs,

with a thermostat included in the electric circuit. Thermometers extended into the box through holes in the top, and for smaller animal work were also placed near the floor of the box. An electric fan inside the box at one end provided constant air movement to minimize stratification of air in temperature levels. The fan played on soaked towels, to provide a high and fairly constant degree of humidity.

The animals, when placed in the heat chamber at 45° to 50° C., rapidly developed a severe, and often fatal, hyperpyrexia. As their body temperatures mounted, unanesthetized mice and rats went through characteristic changes in appearance and behavior which were closely comparable in the 2 species. At temperatures up to about 40.5° C. (105° F.) the animals showed a markedly flushed skin and increasing excitement. Above this level, and up to about 42° C. (108° F.), they were less active and their movements poorly coordinated. Often they waddled. Hyperpnea was extreme. The skin was violently flushed and petechiae appeared, especially in the ears. At about 43° C. (110° F.) they exhibited convulsions followed by coma. In the mouse these convulsions were usually abrupt in onset. They were clonic seizures and were often associated with an erect, stiff, pointed tail. Unless the hyperpyrexia was quickly terminated the animals then died. The flush of the skin usually gave way to an ashen gray pallor. If the animals had remained conscious up to the time of this color change, with it they became comatose, flaccid, with depressed respiration—a picture of extreme vascular collapse.

Only anesthetized dogs were heated. With increasing hyperpyrexia they, too, showed red, hot skin, hyperpnea, and finally vascular collapse and body temperatures of 42° to 44° C.

Aside from the alterations in sweating the clinical picture seen in these animals corresponds closely to that observed in man.

The reduction of hyperpyrexia was studied chiefly in white albino rats. Each rat was heated in the chamber up to the point of coma, when it was quickly removed. An ordinary laboratory thermometer of free-fall type was then inserted through the rectum into the colon so deeply that the bulb lay near the splenic flexure against the diaphragm. After the initial temperature read-

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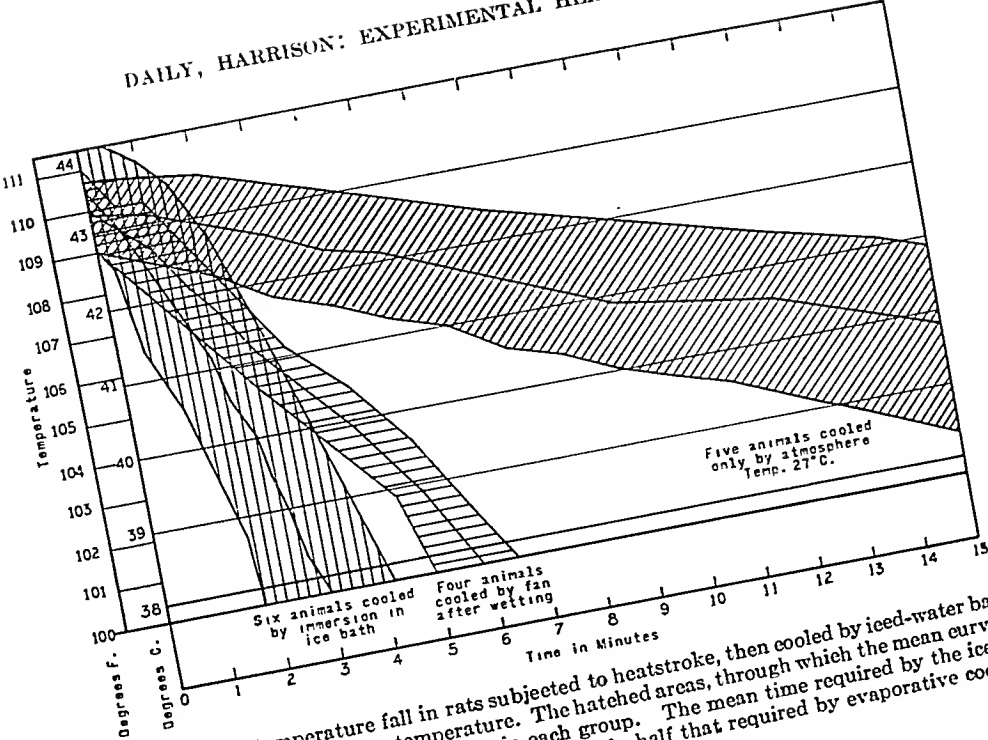


FIG. 1.—Graphs of temperature fall in rats subjected to heatstroke, then cooled by iced-water bathing, by evaporation, and by air at room temperature. The hatched areas, through which the mean curves run, show the extremes of the temperature curves in each group. The mean time required by the iced bath to reduce body temperature to normal was approximately half that required by evaporative cooling.

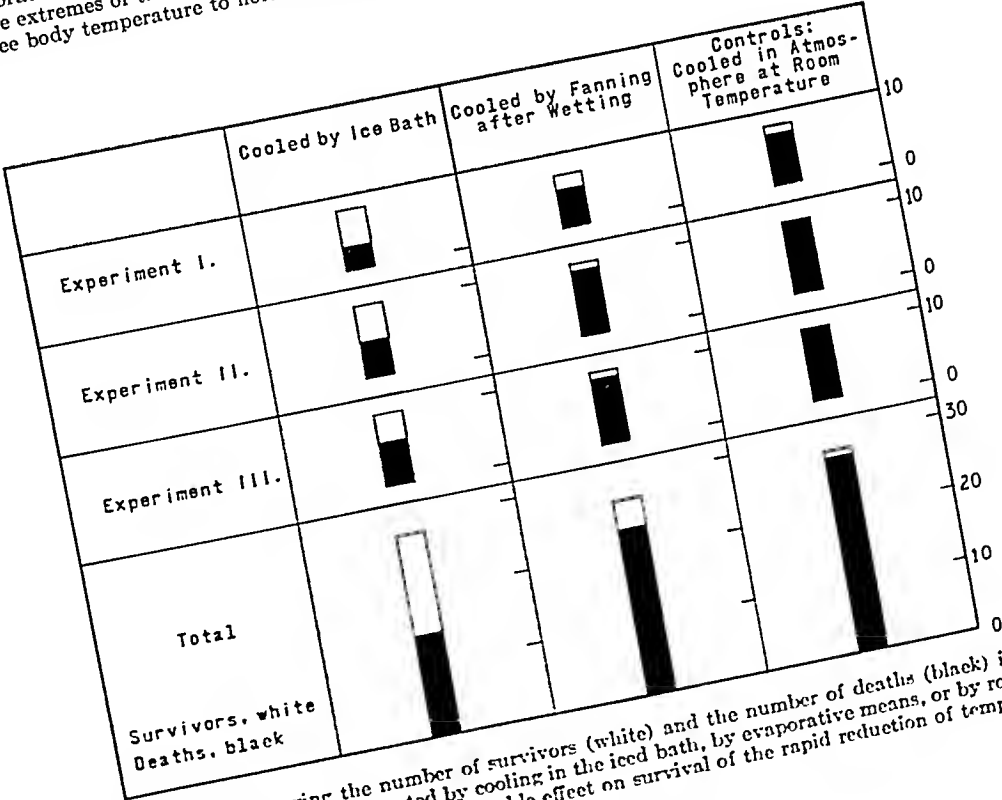


FIG. 2.—Chart showing the number of survivors (white) and the number of deaths (black) in mice subjected to heatstroke, then treated by cooling in the iced bath, by evaporative means, or by room air. Each experiment clearly showed the favorable effect on survival of the rapid reduction of temperature produced by the iced bath.

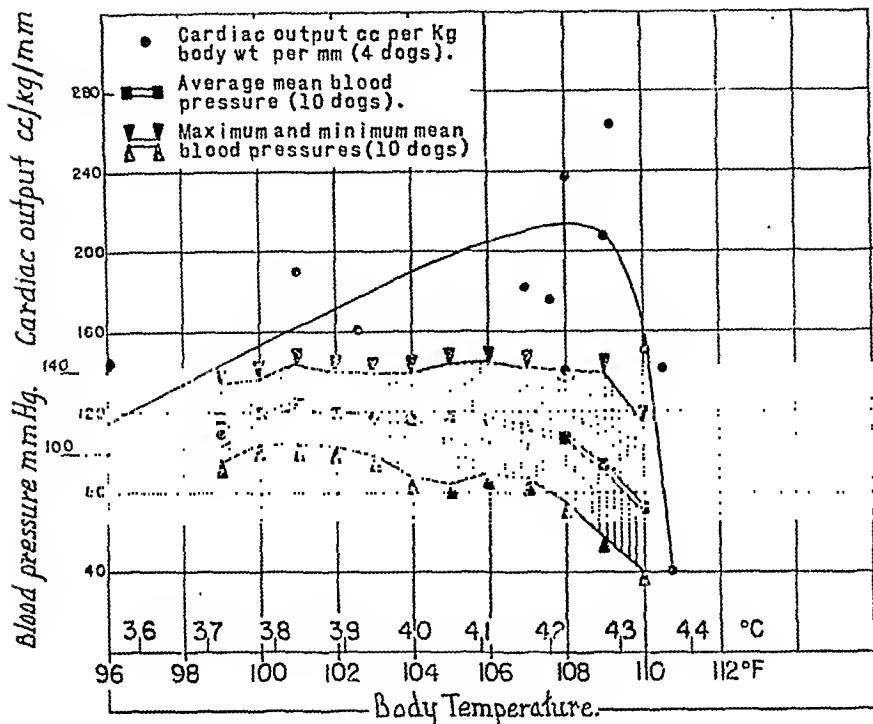


FIG. 3.—Chart showing changes in cardiac output with increasing pyrexia. The dots show actual determinations; the curved line the apparent change. Also shown are mean blood pressure changes. The extremes in 10 dogs, and the average, are shown. The fall in blood pressure precedes the fall in cardiac output.

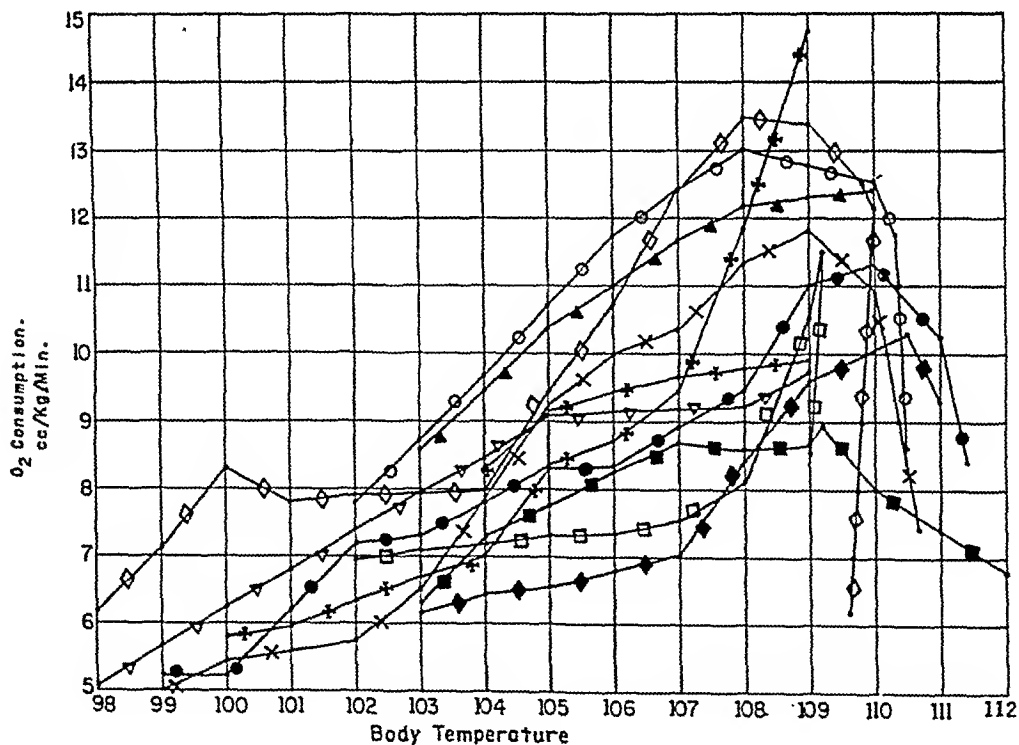


FIG. 4.—Chart showing changes in oxygen consumption with increasing pyrexia. Oxygen consumption rises in a linear fashion with body temperature until circulatory failure occurs. Then, despite continued great need because of sustained pyrexia, oxygen consumption falls sharply. The decline in oxygen consumption is an index of circulatory failure. Each symbol represents a different dog. One dog died suddenly of respiratory failure without prior evidence of circulatory failure; all others showed profound circulatory failure before death by respiratory failure.

ing, 43° to 44° C. (109° to 111° F.), they were cooled in 1 of 3 ways. In a control group the temperature was allowed to fall spontaneously at room temperature of 26° C. A second group was soaked with cold tap water, and then placed directly in the blast of a powerful, 16 inch electric fan. A third group was immersed, except for the head, in ice water. The results are shown in Figure 1. It will be noted that without overlapping in temperature curves, the rate of temperature reduction in the animals cooled

ered the temperature to 38° C. in less than one-half the time required by the fan. Similar results, indicating much more rapid reduction of hyperthermia by the ice bath than by evaporative cooling, were obtained in 2 pairs of dogs, each pair of comparable weight. In both rats and dogs, either the evaporative or the ice-bath cooling, but particularly the latter, tended to produce marked hypothermia.

2. Survival of mice heated to the convulsive endpoint and cooled either by the ice

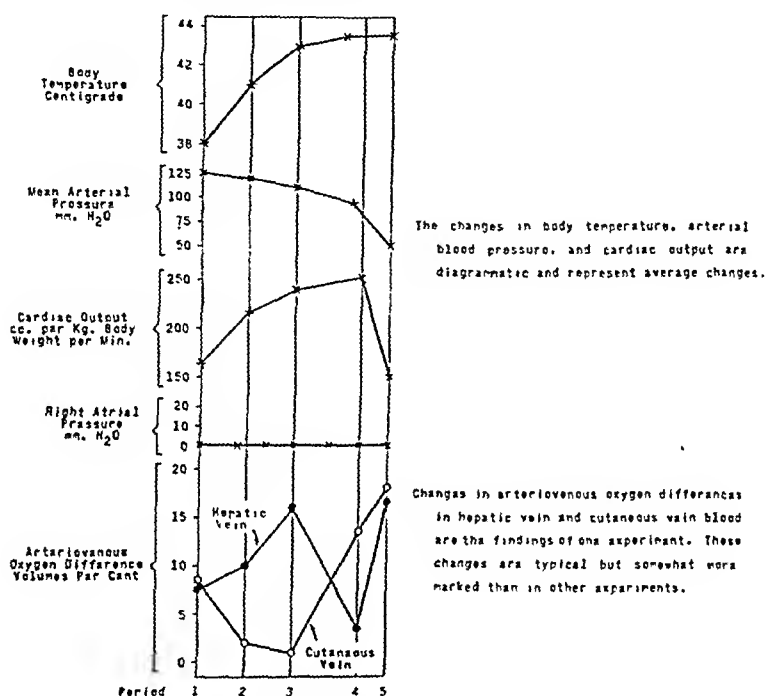


FIG. 5.—Diagram of observed circulatory changes during progressive heat pyrexia in dogs. Period 1, control. Period 2, moderate pyrexia, early "red" stage. Period 3, severe pyrexia, "red" stage; the difference between arterial and skin venous blood oxygen is small, while the A-V difference in hepatic vein blood is large. Period 4, gray stage; there is a tendency toward reversal of the A-V differences noted in the preceding stage, indicating a difference in blood distribution. Period 5, terminal state, late "gray" stage, with profound circulatory failure.

by evaporation greatly exceeded that of the air-cooled animals, while the most precipitous reduction of all occurred in the animals cooled in the ice bath. The curves of 2 rats whose temperatures went to 44.5° C. (112° F.) before coma developed, and who immediately manifested severe vascular collapse, apparently of equal degree, are not included in Figure 1. One was cooled by evaporation, the other by the ice bath. The temperature curves, although both of more gentle slope, showed that in these animals in vascular collapse the ice bath low-

bath, or by the wetting and fanning technique, was compared with that of mice cooled spontaneously at room temperature. The mice, individually, were placed in the heat chamber in small cages, about 5 minutes apart. Each was removed when he began to exhibit involuntary movements. Every third animal removed from the chamber was in turn ice-bath cooled, evaporatively cooled, or simply allowed to cool spontaneously at room temperature. The few animals which died in the first 3 minutes after removal were discarded from the series. Because of

the impracticability of taking rectal temperatures on mice during convulsions, it was decided to fan each of the wetted animals for 2 minutes, and to keep the ice-bathed ones in the bath for 30 seconds. The effect of the ice bath was powerfully sedative on the mice. They became quiet and somnolent within a few seconds. To minimize the severe hypothermia produced by these methods, the mice were then placed in a water bath at 37° C. for 2 minutes. After this they were placed in cages at room

periment. Oxygen consumption was measured by a Benedict-Roth basal metabolism machine attached to a cannula secured into the trachea. The cardiac end of the left carotid artery was used for recording mean blood pressure through a mercury manometer. The cephalic end of the same artery was used for obtaining arterial blood samples. Through a long, metallic cannula inserted through the right external jugular vein, blood samples were drawn from the jugular vein, right atrium, or hepatic vein.

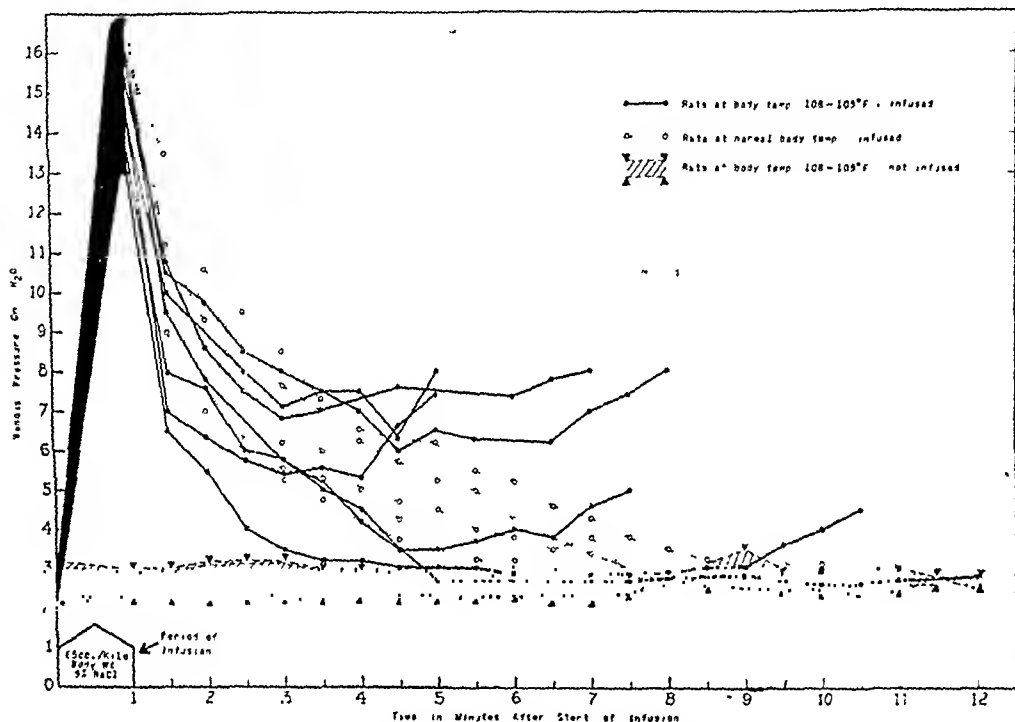


FIG. 6.—Curves of venous pressure in rats following a massive infusion, 65 ml./kg. of normal saline in 1 minute. The dotted lines are the curves obtained from rats at a normal body temperature. After an initial marked rise, their venous pressures fell to normal and remained there. The solid lines are the curves of rats infused during marked pyrexia. Falling almost back to normal after the infusion, the venous pressures rose again. This secondary rise was accompanied by falling arterial pressure, and continued until the animal's death in congestive heart failure. At the bottom of the chart the hatched area includes the venous pressure curves of rats in extreme pyrexia, but not infused. As in the dog, these venous pressure curves are flat.

temperature and observed for survival. The results (Fig. 2) show that only 1 of 28 controls survived more than 24 hours; that 4 of 27 evaporatively-cooled animals survived a like period; while 16 of 28 ice-bathed animals survived.

The mechanism of circulatory collapse was studied in mongrel dogs, anesthetized either with morphine or sodium pentobarbital, and subjected to heatstroke. The head of the dog was allowed to project from the chamber for convenience in attaching and manipulating cannulae throughout each ex-

periment. With large dogs it was not difficult to manipulate this cannula from the hepatic vein to the right atrium and back during an experiment. Blood samples of 5 to 10 ml., collected anaerobically, were replaced with an equal volume of saline.

Venous pressure was measured directly by a saline manometer, equilibrated by free flow through the metal cannula with the blood. The zero point was taken as the level of the right auricle, which was determined at autopsy. Blood oxygen determinations were made by the Van Slyke-Neill

method. The body temperature was measured by an ordinary clinical thermometer in the rectum.

The clinical picture of the dogs in heat-stroke could be correlated with changes in circulatory dynamics. As hyperthermia developed in the dog, the skin became a bright pink, as in rats and mice. After vascular collapse set in there was a definite change through a dusky red to a pallid gray. The gray stage was more prolonged in the dog than in smaller animals. The skin of only

sure in all dogs were essentially flat, for significant change was not observed. In no case was circulatory failure attended by a rising venous pressure unless massive saline infusions were given. The mean venous pressure before hyperthermia was induced was -1 to $+3.5$ cm. of water in 10 dogs. The maximum deviation from this value was about 4 cm. of water.

Mean arterial pressure changes were observed in 13 dogs. As seen in Figure 3, in the early stages of hyperpyrexia the arterial

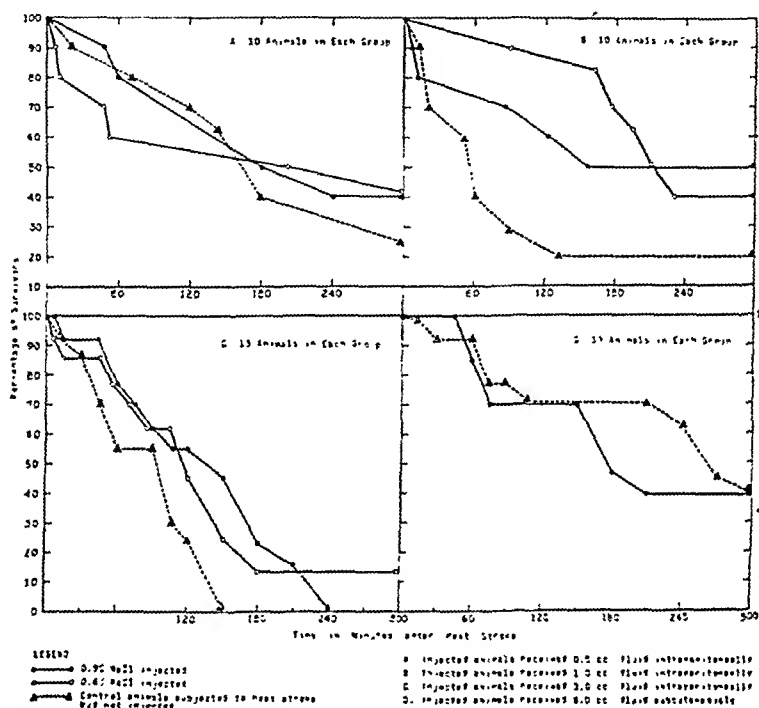


FIG. 7.—Chart showing survival rates of mice in heatstroke, injected with saline fluids. *A*, In a dose of 0.5 ml., neither 0.6% nor 0.9% saline produced a significant increase in survival rate over that of uninjected controls. *B* and *C*, Mice receiving saline in doses of 1 ml. and 3 ml. survived longer than controls. *D*, Mice injected with 6 ml. of 0.9% saline showed no benefit, and probably harm, from this dosage. No difference in favor of either 0.6% or 0.9% saline solutions is apparent.

1 dog was noted to remain pink until death. Beginning at body temperatures of 38°C . (100°F .), to 40°C . (104°F .), depending on the depth of anesthesia, hyperpnea became progressively more extreme. Impending death was indicated by diminution in the vigor of respiratory effort. Death by respiratory failure occurred in all dogs except one.

Pressure in the right atrium, or in the major veins within the thorax, was frequently determined in 10 dogs during all stages of heatstroke. Curves of venous pres-

sure tended to remain near the basal level. With increasing hyperthermia the pressure fell gradually. With severe heatstroke, and particularly in the gray stage, hypotension became extreme.

Cardiac output, as measured by the Fick principle, using venous blood from the right atrium, was determined in various stages of hyperthermia in 4 dogs. The results are summarized in Figure 3. It will be noted that cardiac output approximately doubles as the temperature rises from 37° to 42°C . Beyond that temperature it declines sharply.

✓Oxygen consumption, as shown in Figure 4, was found to rise in a roughly linear fashion with rising body temperature. At temperatures of 42.4° to 44° C. (108.5° to 111° F.) oxygen consumption began to decline sharply despite sustained or rising hyperthermia. Such a fall could only mean marked tissue anoxia. ✓Because it is coupled with severe hypotension and low cardiac output, this decline in oxygen consumption, in the face of sustained high oxygen need, may be considered another manifestation of circulatory failure, and an index of its severity. ✓

Oxygen content of arterial blood, and of venous blood from the right atrium, was determined for calculation of the cardiac output. In addition, the difference between arterial blood oxygen, and the oxygen of blood drawn from superficial veins, for example, the facial—draining chiefly the skin—was determined as an index of flow through the skin in relation to blood need. Similarly, arteriovenous blood oxygen differences in hepatic vein blood were determined as an index of splanchnic blood flow in relation to blood need. The changes encountered are illustrated in Figure 5. It will be noted that at the height of the hyperthermia, prior to circulatory failure, there is a very low arteriovenous difference in the cutaneous venous blood, while in the stage of circulatory collapse the arteriovenous difference is very large.

On the other hand, the hepatic vein blood displayed, during the stage of cutaneous dilatation, a high arteriovenous difference which tended to diminish (to a lesser degree in most of the experiments than in the one illustrated in Figure 5) as circulatory collapse developed. These reciprocal alterations can perhaps be best accounted for by assuming that, initially, there was compensatory splanchnic constriction, followed later by splanchnic dilatation as the result either of thermal injury to the centers in the brain, or of the accumulation of metabolites in the abdominal viscera. Once this state of visceral vasodilatation supervened the blood pressure declined sharply, cutaneous flow diminished, and death soon followed.

✓These results indicate that circulatory collapse induced by pyrexia is ordinarily of peripheral rather than cardiac origin.

The Effect of Heat Pyrexia on Cardiac Reserve. This question was studied by observing the response of the venous pressure to

massive, sudden intravenous infusion in rats with and without pyrexia. Rats were anesthetized with sodium pentobarbital, the peritoneal cavity opened and cannulae inserted into the distal abdominal portions of the aorta and inferior vena cava. Comparisons were then made of the responses of heated (to approximately 43.5° C.) and unheated rats, to the infusion of 0.9% sodium chloride, in doses of 65 ml. per kg. of body weight given over a period of 1 minute. This amount was found to be the maximum which could be tolerated when infused at this rate.

As seen in Figure 6, the immediate effect on all animals, of this infusion, was to cause a sudden marked rise in venous pressure. This was coupled, in most instances, with a rather marked fall in arterial pressure. Most of these pressures quickly reverted to normal. Five rats at normal body temperatures then remained "compensated" for a period exceeding 30 minutes. Seven rats heated to 42° to 43° C. before the infusion showed no such tolerance to this increase in the circulating blood volume. After the initial fall of the venous pressure back to, or nearly to, normal levels, they showed a secondary rise which continued until death. This secondary rise was coupled with a falling arterial pressure and autopsy showed massive pulmonary edema. Five animals similarly heated but not infused showed no such evidence of congestive heart failure. Their deaths were ushered in by a falling arterial pressure without change in venous pressure.

✓These results indicate that while the circulatory collapse of pyrexia is usually of the peripheral type, the reserve power of the heart is impaired, and that heart failure may be induced when sufficient fluid is administered at a sufficiently rapid rate. In patients with preëxisting cardiac disease it might be expected that heatstroke might lead to cardiac rather than peripheral failure. ✓

The Effect of the Administration of Fluid on Survival. Mice, weighing about 25 gm., were heated to the point of convulsions, and various amounts of fluid (0.9 or 0.6% sodium chloride) were immediately administered intraperitoneally to one-half of the animals, the period of survival being compared with that of the untreated controls. As shown in Figure 7, the administration of 0.5 ml. of saline appeared to have no significant effect on survival, doses of 1 to 2 ml. were followed by in-

creased duration of survival, while larger doses were ineffective. These findings, when coupled with those already mentioned, suggest that while the administration of fluid in moderation may tend to overcome the peripheral circulatory failure of heatstroke and, hence, exert a beneficial effect, the administration of larger amounts may tend to induce heart failure and, hence, to exert a harmful effect. The observations on rats, mentioned in the preceding paragraph, would suggest that such a harmful effect was the result of heart failure. Since, however, measurements of venous pressure and other circulatory functions were not made in the mice, the apparently harmful effects of large amounts of fluid cannot be ascribed with certainty to heart failure in this species.

The Effect of Digitalis. Experiments on more than 100 mice, and a number of rats, yielded inconclusive results. This was not surprising, in view of the known resistance of these animals to digitalis. Mice given digitoxin* (2 mg. per kg. of body weight, in proylene glycol, intramuscularly) 2 hours prior to the induction of heatstroke displayed a higher survival rate than controls. However, these mice were found to develop convulsions while being heated somewhat more quickly than the controls, and hence had, on the average, a shorter period of exposure to heat. Mice treated with digitalis after the onset of heatstroke exhibited an increase in survival rate, but the time before death was in most instances too brief to allow for the full effect of the drug. Hence, no conclusions concerning the possible efficiency of digitalis can be drawn from these experiments.

Discussion. The disturbance of function essential for the production of heatstroke is that heat gain exceed heat loss. In these animals, increased heat gain from the environment could not be met by their relatively inefficient heat dissipating mechanisms. In man, large increases in environmental temperature are readily borne by his efficient heat dissipation by evaporation of sweat, as long as he continues to sweat. When sweating ceases in high environmental temperature, however, his remaining mechanism (*c. g.*,

evaporation in the respiratory tract) is inadequate, and his heat gain exceeds heat loss. The validity of considering the state produced in these animals as true heatstroke, comparable to that observed in man, need not be questioned because of the fact that in the normal state man and these animals have different heat dissipating mechanisms.

✓ In the experimental animal heatstroke may be conveniently divided into (1) the premonitory stage, (2) the pink stage, and (3) the gray stage. The premonitory stage is characterized by progressive excitement with rising temperature. Respiratory movements progressively increase in rate and amplitude. Cutaneous blood flow is increased. Cardiac output rises as oxygen consumption keeps pace with rising body temperature. In the pink stage, which is divided from the former by the onset of coma or convulsions, the increase in cutaneous circulation is extreme, and becomes almost equivalent to an arterio-venous shunt. The greatly diminished peripheral resistance in superficial areas permits very rapid venous return, which in turn produces increased cardiac output. This increased venous return would ordinarily produce an elevation of venous pressure, except for the fact that vigorous inspiration is performed so many times per minute. Each inspiratory act increases venous return, at the same time lowering venous pressure in the thorax. This enormous skin circulation can occur only so long as a significant proportion of total blood volume is prevented from entering more voluminous splanchnic areas.

In the gray stage, splanchnic constriction has failed. It is likely that thermally damaged vasomotor centers are no longer able to effect it, and that the accumulation of acid metabolites during the period of diminished splanchnic flow also plays a rôle. When internal vasodilatation is added to superficial dilatation, venous return is no longer great, because of pooling of the blood in dilated capillaries

* We are indebted to Dr. K. K. Chen, of the Eli Lilly Company, for the crystalline digitoxin used in this study.

everywhere. Cardiac output rapidly declines. Blood pressure falls to true shock levels. Oxygen consumption falls for want of transport. To thermally damaged cells all over the body, requiring increased oxygen because of thermally stimulated metabolism, is added the insult of circulatory anoxia. The animal is in profound peripheral vascular collapse.

Why is pulmonary edema encountered in patients? Pulmonary edema was not observed in these animals, and apparently they did not develop heart failure, unless given saline infusions. No changes in venous pressure were observed. Four possible mechanisms are suggested.

1. In the pink stage cardiac work is increased. The senile hearts of old victims may fail under this strain, while the laboratory animal's heart does not.

2. Venous return and pulmonary flow are greatly increased. Of necessity, this means pulmonary hyperemia. Pulmonary capillaries are thermally damaged and, perhaps, increased in permeability. Rapid and vigorous respiratory effort means more inspiratory negative intra-alveolar pressure per minute. This lowering of the mean intra-alveolar negative pressure would tend to pull fluid through engorged damaged capillaries.

3. Pulmonary edema may conceivably develop as a final manifestation of peripheral circulatory failure, the diminished coronary flow consequent to the lowered arterial pressure eventually leading to heart failure. This sequence of events was not observed in our animals.

4. Pulmonary edema may develop because of overenthusiastic treatment with intravenous fluids. A review of clinical records of fatal cases in our clinic suggests this. Rats with hyperthermia certainly tolerated large intravenous infusions less readily than those at normal temperatures.

It is universally accepted that the termination of hyperpyrexia, as quickly as is consistent with safety, is indicated. By the use of evaporative cooling a fairly rapid reduction of hyperthermia in the rat and dog was obtained. By ice-bath cool-

ing, even more rapid cooling is achieved. Since the effect of an elevated temperature on body proteins depends on the time as well as the temperature, the shortening of the duration of hyperpyrexia by even a few minutes may mean the difference between reversible and irreversible brain damage; between mild and profound circulatory failure. It was noted above that there are 2 criticisms of the ice-bath in the literature: that it is less effective than evaporative cooling because of physical principles, and possibly skin vasoconstriction, and that it may be dangerous, producing "shock." Our experiments on the rate of temperature reduction in the rat and dog deny the first objection, and the greater survival of mice treated with ice-baths, as compared to those treated by evaporative cooling, denies the second. Theoretical objections to the ice-bath, on the basis that melting 1 gm. of ice removes only one-seventh as many calories as evaporating 1 gm. of water, are untenable. On the hospital ward, the object is not to obtain maximum cooling with a given number of grams of ice or water. The object is to obtain most *rapid* cooling regardless of the amounts required.

It seems apparent that after reduction of hyperthermia, if vascular collapse is present, this, too, must be treated. The vascular collapse is primarily peripheral, due to underfilling of a generally dilated capillary bed, but probably the heart is racing toward failure, too. Lacking pharmacologic means to correct capillary vasodilatation, one can treat the vascular collapse only by intravenous fluids. One does so apparently at the imminent risk of producing heart failure and pulmonary edema.

On the basis of these studies, the following outline of treatment is suggested as trial-worthy.

1. Heatstroke is a grave emergency, and when the diagnosis is tentatively established (by the coexistence of [a] a history of exposure to excessive environmental temperature; [b] otherwise unexplained

pyrexia; [c] dry skin) immediate therapy should be instituted.

2. If the patient is comatose, or if body temperature is above 41° C. (106° F.), the patient should be immersed in ice-water. Milder instances may be treated by evaporative cooling. The oral temperatures should be followed minute-by-minute during the process of cooling.

3. At an oral temperature of about 38.5° C. (101° F.) the patient should be moved to a tub of water at about 38° C., the body temperature still being observed continuously. After the patient's body temperature has stabilized at an essentially normal level, hydrotherapy may be discontinued.

4. If manifestations of shock—gray skin color, slow filling of blanched areas, poor filling of veins behind a tourniquet, severe hypotension—are present, infusions must be given, but with great caution, the venous pressure, state of breathing and breath sounds being continuously observed. Rapid digitalization is probably indicated if pulmonary edema or rising venous pressure develop.

5. Oxygen therapy is probably valuable when either peripheral failure or pulmonary edema is present.

6. After the emergency state has passed, the patient's temperature must still be watched very carefully. Adequate attention should be given to fluid and electrolyte requirements.

Summary and Conclusions. Heat pyrexia (heatstroke) has been produced in laboratory animals (dogs, rats, mice) by exposure to high environmental temperatures. Except for differences related to the sweating mechanism, and the more rapid course of events in smaller animals, the clinical picture of heat pyrexia in animals resembles closely that seen in man.

In the "pink stage" heatstroke is characterized by greatly increased cutaneous blood flow, amounting practically to an arteriovenous shunt, with compensatory internal constriction. Cardiac output is high.

In the "gray stage," or stage of vascular collapse, generalized vasodilatation produces peripheral circulatory failure. Venous return and cardiac output fall. Despite continued need, oxygen consumption declines for want of transport. Anoxic damage is added to thermal damage in the body cells, generally.

Hyperthermia is reduced most rapidly, and with greatest advantage to the animal's chances for survival, by the ice-bath.

Fluids in moderate doses produced increased survival time in mice subjected to heatstroke.

Massive intravenous infusions produced heart failure in rats during hyperthermia, while the same infusion was well borne by the rat at normal temperature. This indicates a definite reduction of myocardial reserve at excessive levels of body temperature.

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STUDIES ON THE ACTION OF INTRAVENOUSLY ADMINISTERED SODIUM AMYTAL*

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EARLIER studies have shown that the administration of relatively small doses of sodium amytal may be followed by profound alteration in a subject's reaction to pain.³ Furthermore, tension headaches and other sensations resulting from an increase in contractile state of muscles may be reduced in intensity or abolished.^{13,15} Sensation and motor power may be restored in hysteria.⁸ The blood pressure of hypertensives may be greatly lowered,^{1,14} and, following intravenous injection of sodium amytal, there has even been reported relief of asthmatic attacks.⁶ There have been numerous investigations of the mechanism of action of sodium amytal^{5,7,10,11,12,16,17} but explanation of the phenomena referred to has not been established. Accordingly, and in view of the currently wide use of the drug, a series of observations concerning its action was undertaken.

Method. Seven hundred patients selected at random from the clientele of the medical psychiatric wards and out-patient departments of 1 civilian and 2 military hospitals served as subjects. During the course of their investigation and management they were interviewed 1 or more times following intravenous injection of from 0.1 to 0.5 gm. of sodium amytal in a 10% solution administered at the rate of approximately 1 cc. per minute.

Observations. 1. **EFFECT ON PAIN PERCEPTION.** Using the pain threshold measuring device of Hardy, Wolff and Goodell,⁴ 4 subjects were tested before and 15 minutes after injection of 0.5 gm.

of sodium amytal. It was found that, as described elsewhere with other barbiturates,¹⁸ sodium amytal did not raise significantly the threshold for perception of pain. In Figure 1 is contrasted the threshold raising effects of 0.3 gm. acetylsalicylic acid with that of 0.5 gm. sodium amytal.

Comment. It may be inferred from these data that whatever salutary effects may follow the administration of sodium amytal in painful conditions, they do not stem from the blocking of pain perception. They must occur either because of alterations in the reaction of the subject to the painful experience or from interruption of the mechanism responsible for the noxious stimulus.

2. **EFFECTS ON ATTITUDES AND EMOTIONS.** The most obvious changes among the 700 subjects to whom the drug was administered resembled those which might be expected following ingestion of alcohol. Usually the subject became relaxed and jocular but if disturbing topics were introduced and dwelt upon in the interview the subject gave more evidence of being distressed by them than he did when he was not under the influence of the drug. In addition to the intensity of the focus of the subject's attention on the topic at hand, there was a distractibility which made it possible to shift the focus to other topics by appropriate manipulation of the situation. Thus, a subject could often be made tense and tearful at one moment and relaxed and jocular the next.

* Investigation was carried out under fellowship grants from the Commonwealth Fund and the Hoffheimer Foundation.

Comment. While intravenous injection of sodium amytal is likely to be followed by relaxation and freedom from anxiety, it is not necessarily so. The drug induces in the subject a state of pliability in which relaxation and freedom from anxiety readily occur when the setting is secure and friendly, but in which tension and anxiety occur with equal ease when the security of subject is threatened by the introduction of disturbing topics.

"insane." Later, in several subjects tension headaches were relieved by injection of sodium amytal and were then reinduced while the subject was still under the influence of the drug, by the introduction of troublesome topics into the discussion.

4. HYPERTENSION. During interviews with fully conscious individuals who have hypertension it has often been possible to alter the level of blood pressure by alternately disturbing and reassuring the sub-

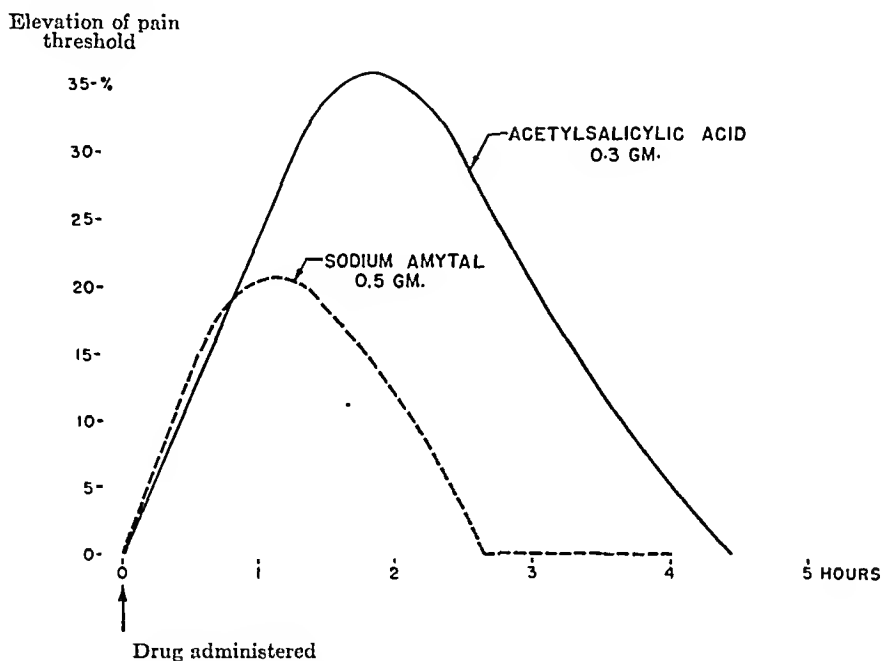


FIG. 1.—Minor pain threshold raising effect of sodium amytal 0.5 gm., administered intravenously, compared with effect of acetylsalicylic acid 0.3 gm., taken by mouth.

3. TENSION HEADACHE. Prompt abolition of tension headache by muscular relaxation induced with the aid of sodium amytal has been observed in 45 subjects. In one subject, however, who was not having a tension headache at the time of injection, headache occurred during administration of sodium amytal. She appeared anxious and harassed with furrowed brow and an expression of anguish. She revealed that she had been concealing from the examiner the fact that she had once been a patient in a mental hospital. She felt torn by the conflict between her obligation to tell everything and her fear that the examiner would drop her case if he knew of her having been once considered

ject.⁹ It was found that in subjects under the influence of sodium amytal such manipulations were far easier than they were when applied to unnarcotized individuals.

The ease with which blood pressure could be modified in hypertensive subjects after intravenous injection of sodium amytal is apparent in the following case.

Case Reports. CASE 1. A 41 year old married Jewess had hypertension since a pregnancy 10 years before. The hypertension had been sustained at a level of approximately 210/130 for 1½ years prior to her visit to the New York Hospital. She complained of frequently recurring headaches, "like a tight hat" associated with irritabil-

ity and fatigability. Her conflicts concerned mainly her relationship with her parents and her husband. Her mother had been strict and humorless, giving very little affection and support either to her husband or to her daughter. Her father was also tense but kinder and more loving. Both parents had hypertension. The patient throughout her life had felt heavily dependent on her father and resentful of her mother, but she nevertheless continually felt the need to appease the latter and gain her approval. She married at 24 a man 4 years older than herself upon whom she depended heavily as she had on her father, but toward whom she also felt resentment because of his relatively poor earning power. Her general demeanor was one of cheerful self-possession and none of her anxieties and conflicts were apparent when she was in her fully conscious state.

Sodium amytal, 0.3 gm., was administered intravenously. Before the injection blood pressure was 255/125. Under the influence of the drug she became well relaxed and began to talk freely. Blood pressure fell to 170/110. When she recalled an experience in which she received a telegram which she was reluctant to open because she feared that it might tell her of her husband's death, her blood pressure rose to 195/130. It subsequently fell to 180/120. She next mentioned her hatred for her mother and her father's death. Blood pressure rose to 230/150. It fell to 180/120 when the conversation was turned to the possibility of happiness in the future. Later she became very tense, began to sob, saying that her mother had killed her father by her bad treatment of him. Blood pressure rose to 226/134. Again it decreased when she spoke of good times she had had fishing with her father, but when the subject of her father's unhappiness was dwelt upon blood pressure rose again to 238/150. She was finally diverted and began to joke with the physicians. A precipitous fall to 178/120 occurred. While speaking of sexual intercourse being unsatisfactory blood pressure was 220/140. Later, when she laughed and spoke of her enjoyment while playing pinochle it fell again to 188/118. The last 2 readings were 184/140 and 180/125 when she spoke of playing the piano with her daughter (Fig. 2).

In numerous other hypertensive subjects

the blood pressure was made to rise or fall with appropriate stimulation under sodium amytal. Often when the situation was manipulated the blood pressure showed no initial drop following injection but began to climb at once.

CASE 2. A 31 year old married woman whose hypertension had been known to exist for approximately $1\frac{1}{2}$ years illustrates this occurrence. She was a mild-mannered, self-possessed individual who denied all conflicts but whenever the fact that her sister had always been more successful than she was dwelt upon her blood pressure rose. Prior to injection of sodium amytal her blood pressure was 180/120. During injection of 0.3 gm. of the drug she was asked to compare the achievements of her sister's husband with those of her own. She smiled sweetly, retained her composure and stated that her own husband had not done as well as her sister's. "But that doesn't bother me. . . Well, I did expect my husband to do better. When I married him I thought I could make something of him . . . but he treats us very well and it does not bother me at all." By this time her blood pressure had risen to 215/135. After this topic had been dwelt on for 5 minutes she was reassured and allowed to rest. Forty minutes later her blood pressure had fallen to 170/110. The course of the blood pressure during the interview is graphically shown in Figure 3.

5. TURBINATES AND NASAL MUCOSÆ. Other bodily structures which participate in the organism's reaction to situational threats are the turbinates which shut off or open the nasal airways by either swelling or contracting. The relevance of these phenomena to sinusitis and nasal disease has been described elsewhere.¹⁹ The way in which the appearance and function of the nasal structures could be altered experimentally is illustrated by the following account.

CASE 3. A 42 year old woman had suffered from vasomotor rhinitis and chronic sinusitis for 2 years. On numerous occasions the state of her nasal membranes had been correlated with her life situations and attitudes and it had been found possible to bring about either hyperemia, hypersecretion

and obstruction in the nose or subsidence of these changes by suitable discussion.

As discussed elsewhere,⁶ when hyperemia and engorgement of nasal structures was sustained the vasodilatation often subsided and the structures became pale, remaining for a time boggy and edematous looking. This more chronic state of vasomotor rhinitis could also be made to subside during relaxa-

tion under sodium amytal. With discussion of threatening topics, however, the obstructive process could be started up again, hyperemia and hypersecretion ensuing.

In this experiment (Fig. 4) the topic under discussion concerned a major conflict in the subject's life. She was living with her third "husband," by whom she had a daughter, aged 5, without having divorced her second

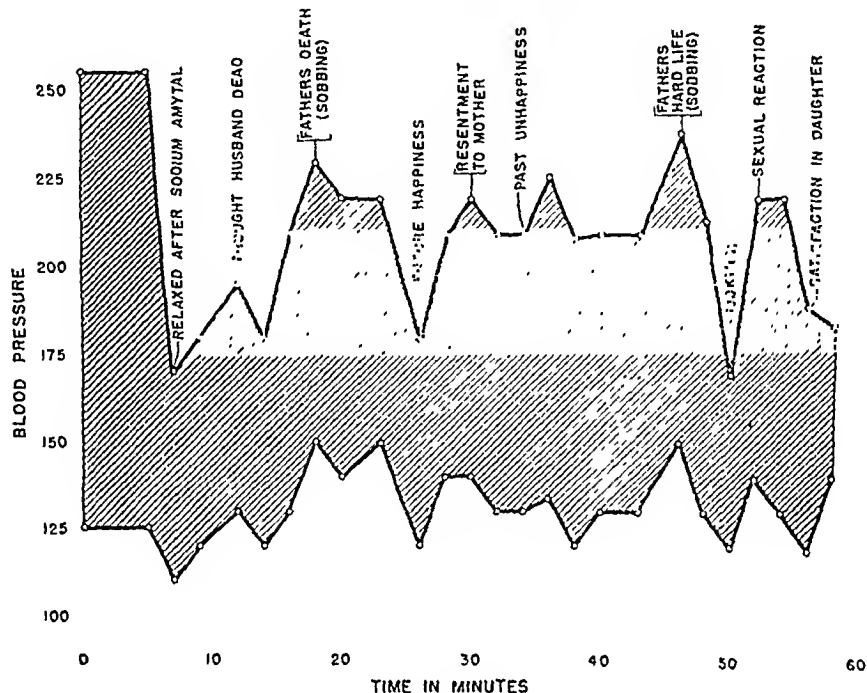


FIG. 2.—Variability in level of blood pressure in a hypertensive subject correlated with changes in topic during interview under intravenously administered sodium amytal, 0.3 gm.

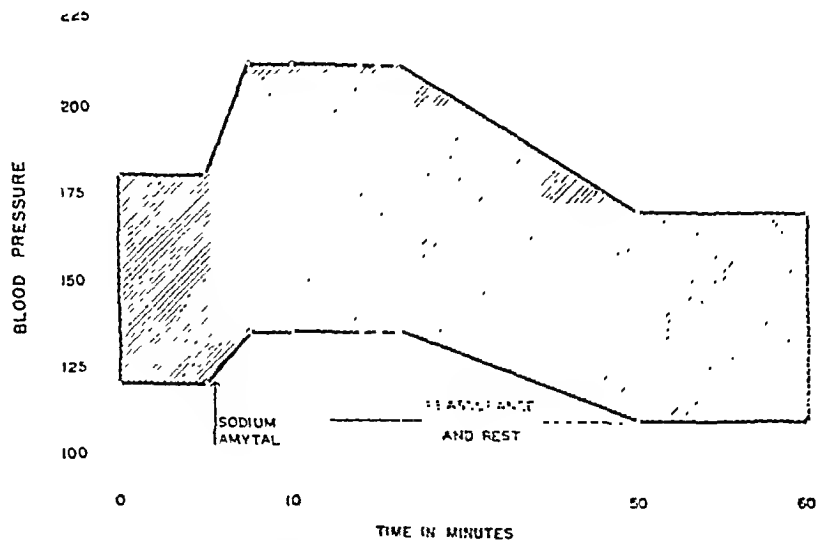


FIG. 3.—Initial rise in blood pressure following intravenously administered sodium amytal during discussion of relevant conflict.

husband. The divorce decree was expected momentarily and she was looking forward to the possibility of marrying her present companion in order to make legitimate her child. At the same time she was reluctant to marry him because he was a poor provider, irresponsible, often drunk and abusive to their child. She feared that continued life with him might be seriously damaging to the girl. She had been in conflict for several days awaiting the divorce decree. Her nose was obstructed, the membranes pale, swollen and wet. During administration of the sodium amytal she was strongly

sodium amytal, as illustrated in the case of the following patient.

CASE 4. A 36 year old housewife complained of attacks of dyspnea, associated with dry cough and wheezing for the previous 6 months. Her parents were Russian Jews, the father lettered and gentle, the mother uneducated and cold; both were forceful characters. Her 3 sisters were married to Jewish businessmen, and 3 brothers were successful as an accountant, a factory foreman and a lawyer, respectively. They all enjoyed the favor of the parents, whereas

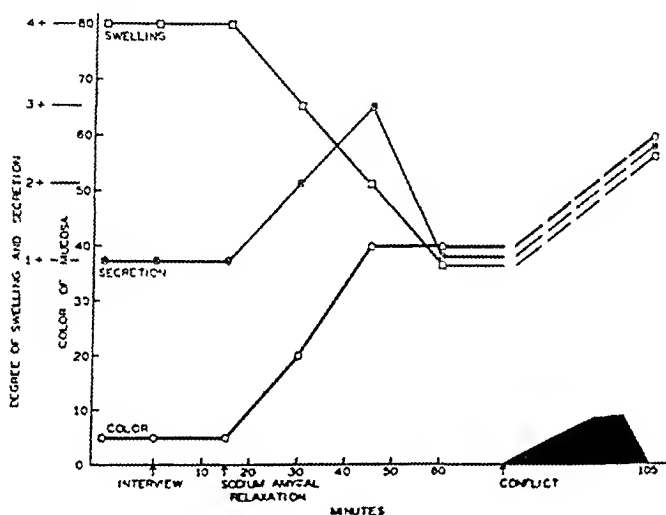


FIG. 4.—Subsidence of nasal obstruction by swollen, pale turbinates during relaxation and freedom from anxiety following intravenous injection of sodium amytal. Note increase in secretion and return of color to the membranes during deturgescence. Latter half of graph shows subsequent hyperemia with hypersecretion, swelling and obstruction during discussion of troublesome conflict.

reassured and offered the support and counsel of the physician. After her membranes had resumed their normal appearance and her airways had opened she was abruptly threatened by unsympathetic discussion and the challenge, "Why do you marry John if he is making a neurotic out of your daughter?" Promptly her nasal membranes became hyperemic and hypersecretive again and the airways became obstructed.

6. **ASTHMA.** In subjects with asthma engorgement of the turbinates with resultant nasal obstruction was found to go hand in hand with bronchial constriction in asthmatic attacks. These changes, too, were found to be subject to manipulation following intravenous administration of

the subject had incurred their disapproval by impulsively marrying a relatively non-competitive Roman Catholic of French-Italian parentage, 9 years her senior.

She was ambitious to improve the social status of their children by educating them despite her husband's meager earnings. Her daughter, at the age of 8, developed diabetes mellitus, which increased the patient's insecurity and further threatened her ambitions. At this time she was becoming increasingly disappointed, anxious and resentful, and had difficulty in breathing through her nose. This nasal obstruction developed suddenly when several women in her presence condemned a girl for "overstepping conventions." It continued and

grew more troublesome and a year later she had nasal polyps removed.

Twelve months later (November 1945) her son became ill with abdominal complaints and the subject feared that he, too, might have diabetes. At this time she developed attacks of wheezing during the night. These increased in frequency until she soon was having persistent respiratory distress with an accompanying dry cough.

50 minutes of this interview. As soon as sodium amytal was injected, however, the changes became greatly accentuated and there occurred marked swelling of the turbinates. Subsequently the subject was reassured and after she had slept for several minutes the nasal structures were noted to have resumed their former appearance.

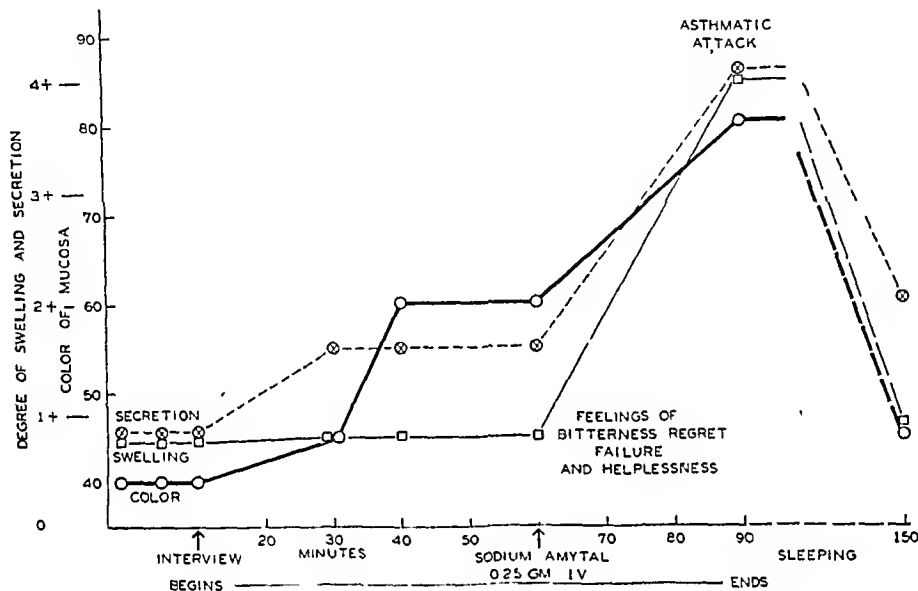


FIG. 5.—Occurrence of hyperemia, hypersecretion and swelling with obstruction in the nose and precipitation of an asthmatic attack during an interview dealing with troublesome conflicts. Note acceleration of the changes following intravenous injection of sodium amytal and subsidence of the changes after reassurance and relaxation.

As reported elsewhere,⁶ it was possible in this subject to induce nasal engorgement, obstruction and hypersecretion with associated attacks of asthma by introducing threatening topics into the conversation. Conversely, when relaxation and feelings of security were induced engorgement of the nasal mucosa and the asthma subsided. Such experimental correlation of situation with symptoms was accomplished most readily when the subject had received an intravenous injection of sodium amytal, as illustrated in Figure 5. The interview in the instance illustrated dealt with her having "cut off her nose to spite her face" in rejecting her family's favor by marrying out of her cultural group, of her husband's failure to have vindicated her decision by "succeeding," and of her thwarted ambitions for her children. Only a small increase in redness and secretion in the nose occurred in the first

7. **EPILEPSY.** Finally, in epilepsy, seizures which are customarily inhibited by barbiturates have been induced in suitable subjects following intravenous administration of sodium amytal during abreaction to the discussion of topics of threatening significance.²

CASE 5. The patient, a 26 year old man, had had psychomotor seizures for 11 years and *grand mal* convulsions for 2. The occurrence of his attacks had been correlated with episodes of intense anger, to which he felt unable to give overt expression. His chief conflict concerned a hatred for his mother whom he felt had not loved him and had failed to equip him for a competitive life. A typical *grand mal* seizure was induced in this subject immediately after the injection intravenously of 0.3 gm. sodium amytal dur-

ing a discussion of his mother in which he became enraged and spoke through clenched teeth saying, "I'll k-k-k-kill her." At the height of this outburst his angry face suddenly became blank and expressionless. He lost consciousness and had a tonic and clonic convulsive seizure. Throughout this procedure electroencephalographic tracings had been made. Typical *grand mal* waves were recorded during the seizure.

Conclusion. It is clear from these data that sodium amytal has no direct predictable effect on the mood and attitude

of the subject. It exerts no direct pharmacologic action on skeletal muscles, smooth muscles or glands which are subject to nervous influence. Thus its designation as a "vasodilator substance" when used to aid in the selection of hypertensive subjects for sympathectomy is a misnomer. On the other hand, it creates in the individual a state of altered consciousness associated with marked suggestibility in which it is often possible to alter not only the emotional reactions of the subject but also the bodily changes that accompany them.

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THIOURACIL AND PROPYLTHIOURACIL IN THE PRE-SURGICAL AND MEDICAL MANAGEMENT OF THYROTOXICOSIS

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THE use of thiouracil and of propylthiouracil* during the past 3 years facilitates their evaluation either as a means of preparing patients for operation, or as a method of medical treatment without recourse to surgery. The earlier studies in this investigation concerned themselves with the problem of finding the earliest time for the initiation of a maintenance dose of thiouracil, in order to preclude the occurrence of agranulocytosis. A plan of study was pursued that integrated the clinical investigation with various laboratory procedures. It was subsequently learned that the susceptible patient would develop agranulocytosis, regardless of the early administration of a maintenance dose and the simultaneous prophylactic administration of "solubilized" liver as a source of folic acid. This phase of the work will be explored further at another point in this paper. The high incidence (15%) of early mild and often transient toxic effects of thiouracil¹³ is not sufficient to deter the clinical investigator from using this drug, but the serious complication of agranulocytosis is a definite threat to its general acceptance. With the advent of propylthiouracil this danger has been sufficiently lessened so that a more favorable comparison may be drawn in the future between the surgical mortality

rate and the undesirable factors accompanying the exclusive use of propylthiouracil. Since the physiologic and pharmacologic effects of thiouracil and of propylthiouracil are similar, the results obtained from the use of thiouracil may be employed as the yardstick to evaluate the newer and less toxic preparation.

Procedure. One hundred patients were employed in this study (Table 1). Of these, 63 received thiouracil and 37 received propylthiouracil. Preliminary to receiving any therapy a basal metabolism test, a galactose thyroid function test, a serum cholesterol determination and a blood count were done on each patient. After the start of therapy and throughout its course a white blood count and differential count were done weekly, or more frequently if the white blood count ranged around 4000. The basal metabolism test, the galactose thyroid function test and the serum cholesterol determinations were done simultaneously every 2 weeks until a maintenance dose was established and then at less frequent intervals. The patients were examined at weekly intervals for the first 3 months and then, after a maintenance dose was established, every 2 weeks for 3 months and then every month. At each visit a white blood count and differential count was done.

The galactose thyroid function test was done in accordance with MacLagan's¹⁰ modification of Althausen's¹ method in which the

* The thiouracil and propylthiouracil used in this study were supplied by the Lederle Laboratories through the kindness of Dr. Stanton M. Hardy.

values of the blood, taken at 30, 60 and 90 minutes after the ingestion of the galactose, are totaled and expressed as the galactose index. Our experience has shown that a range of 50 to 100 may be considered within the normal range. In doubtful cases the consideration of the peaks at 30 or 60 minutes was more informative than the totaled amount.

to be a sensitive indicator to within 24 to 48 hours. The details of this investigation are being presented in a separate report.

Propylthiouracil was employed in a new group of patients and in several of those who exhibited toxic reactions to thiouracil. We found, in agreement with others,¹¹ that a total daily dose of 200 mg. administered in divided doses of 50 mg. 4 times daily

TABLE 1.—ANALYSIS OF CASES INVESTIGATED

Types treated	Exophthalmos	Diffuse toxic	Toxic nodular	Recurred postoperative	Malignant exophthalmos	Non-classified	Total
Thiouracil	6	21	16	14	1	5	63
Propylthiouracil	6	18	7	4	1	1	37
Total cases treated	12	39	23	18	2	6	100

The earliest group of patients was treated with divided doses of thiouracil in July 1944. One-tenth gm. was given 4 times daily, together with 5 capsules of a solubilized liver (Liver "L")* for each 0.1 gm. of thiouracil. As soon as the galactose index approached the normal range the dose of thiouracil was reduced to 0.1 gm. twice daily, as a maintenance dose, regardless of the basal metabolism rate at that time. Those patients that were treated medically were maintained on this dose or less, depending on the individual response, for a period of 9 months to 1 year. After discontinuing the use of the drug, the patients were then seen at regular intervals of 3 to 6 months to determine whether the toxic symptoms had recurred. Those patients that were being prepared for thyroidectomy were treated in the same manner as the medically treated patients. After a maintenance dose had been established in these patients, and both the basal metabolism rate and the galactose thyroid function tests were maintained within the normal range, the use of thiouracil was discontinued. Fifteen drops of Lugol's solution was then administered 3 times daily in order to bring about involution of the gland. The length of time that the Lugol's solution is given is an important factor in facilitating the operative procedure. In order to determine the optimum time for operation, the galactose thyroid function test was employed as a means of indicating whether involution of the gland was complete. This test proved

yielded the optimum therapeutic effect. The same plan was followed to establish a maintenance dose in these cases as was observed when thiouracil was employed. When the basal metabolism rate and galactose thyroid function tests were within the normal range, the dose of propylthiouracil was reduced to one-half the therapeutic dose.

Ten patients, taken at random, were given 5 drops of Lugol's solution twice daily and 50 mg. of propylthiouracil 4 times daily throughout the period of treatment. This was done in the light of the work of Rawson *et al.*¹² in explaining the 2-fold action theory of iodine. They believe that the synthesizing action of iodine, in which it is converted into the thyroid hormone is independent of its involuting action on the gland. Consequently they believed that thiouracil, by inhibiting the production of the thyroid hormone,² separates these 2 functions and allows involution to proceed with the use of iodine at the same time that it blocks the production of the hormone.

RESULTS. The present investigation concerned itself with the dual purpose of evaluating the use of the antithyroid drugs, thiouracil and propylthiouracil, and of applying those known laboratory procedures that would indicate the minimum effective therapeutic dose and the earliest initiation of a maintenance dose of thiouracil. This was originally planned to obviate the toxic effects of thiouracil

* The "solubilized" liver was supplied by the Wilson Laboratories through the courtesy of Dr. David Kline.

because the size of the dose frequently bore a direct relationship to the occurrence of toxic reactions. A review of the various laboratory procedures indicated that the basal metabolism rate is still the simplest method of determining thyroid activity. In spite of this, it is known that there are factors which will increase the basal metabolism rate in patients who do not have an associated overactivity of the gland. Hypertension, congestive heart

iodine became normal before the basal metabolism rate was normal in thiouracil treated patients. The special facilities necessary for performing this test would preclude its universal use by physicians who do not have research facilities available. Therefore, the galactose thyroid function test was chosen as a supplement to the basal metabolism and the serum cholesterol determinations.

Since the advent of the galactose thy-

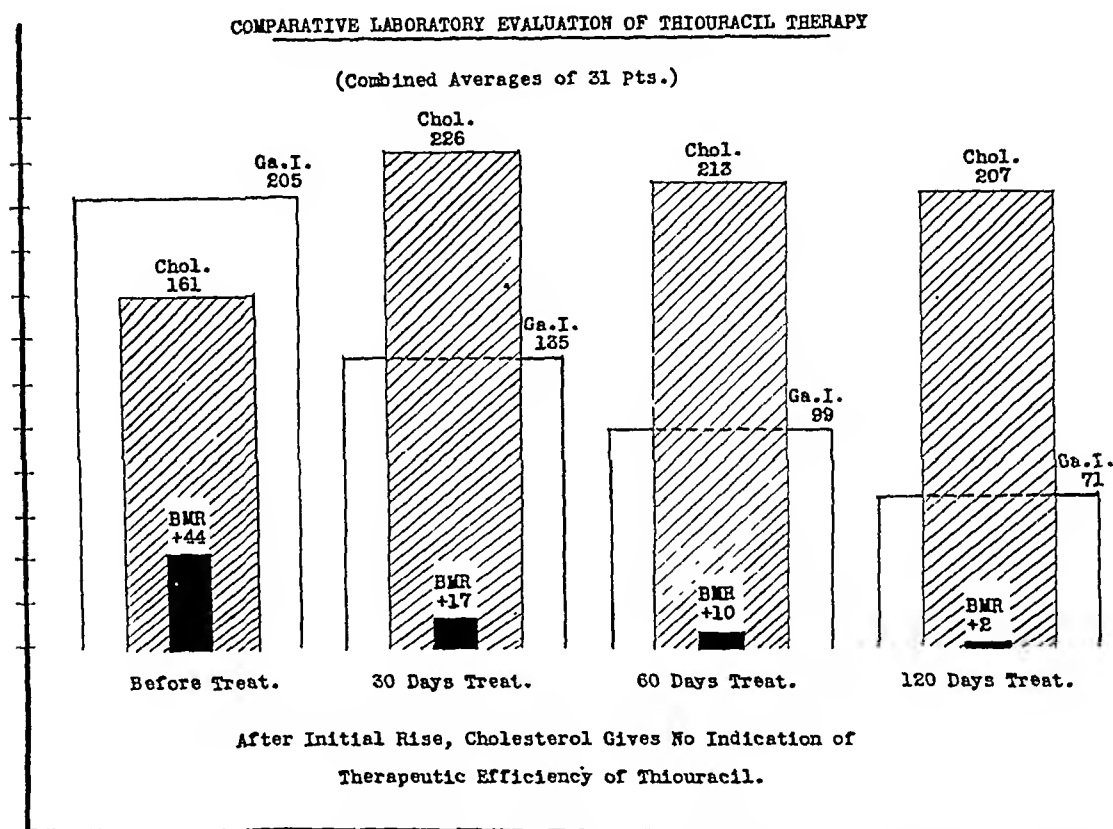


FIG. 1.—The combined averages of the 3 tests that were employed indicate their comparative value in the diagnosis and their value as therapeutic guides in patients treated with thiouracil.

failure, emotional disturbances and mechanical factors sometimes interfere with a proper determination. Lowenstein⁹ suggested that the estimation of the protein bound plasma iodine could be employed as a sensitive indicator of the fluctuation that occurs in the production or suppression of endogenous iodine, thus offering an index to the accurate quantitative measurement of the production of the thyroid hormone. Williams and Clute¹⁷ observed that the plasma protein

roid function test as a procedure to aid in the diagnosis of thyrotoxicosis, varying reports¹⁵ have appeared in the literature regarding its reliability as a diagnostic test in this condition. In the present series the test was of diagnostic value in 70% of the patients. Its value was not limited to those in whom the basal metabolism determination was not sufficiently informative; it was also of value as a means of following the progress of treatment. It was found that in many cases

the galactose index reached normal before the basal rate approached the normal range. It was in these cases, when thiouracil was employed, that this information aided in the earlier establishment of a maintenance dose. Reference to the

been symptom-free for 19 months since stopping treatment.

The degree of sensitivity of the galactose test will vary with the patient. In the case of Patient R. B. the test was an extremely sensitive guide to dosage. Refer-

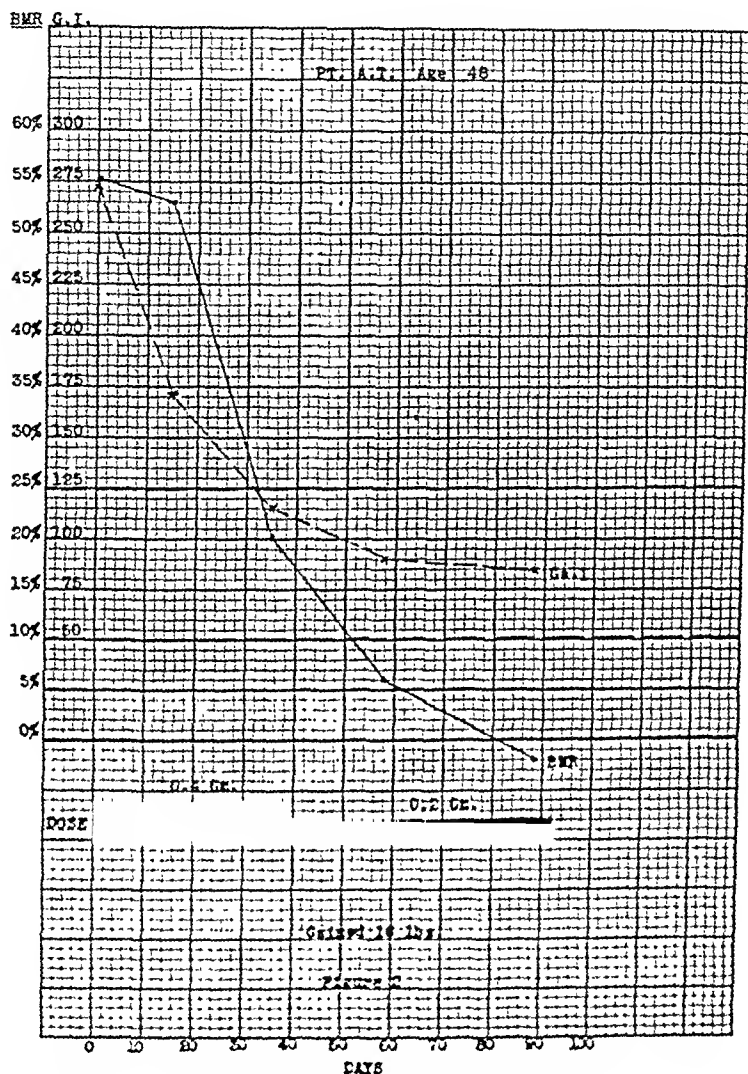


FIG. 2. —Maintenance dose established in 35 days on basis of early return of galactose test. Basal metabolism rate normal in 58 days.

chart of A. T. (Fig. 2) indicates that the galactose index was within the normal range in 35 days while the basal metabolism rate was still $\pm 20\%$. A maintenance dose of 0.2 gm. daily was established and improvement continued. This patient was treated for 12 months and has

ence to Figure 3 will show that when the dose of thiouracil was reduced to 0.1 gm. daily on the 50th day of treatment and maintained at this level for 30 days, the galactose index rose from 35 to 125, while the basal metabolism rate showed a negligible change. When the maintenance

dose of 0.2 gm. was resumed, the galactose test readily reflected the favorable response to this increased dosage by a drop in its value.

The mechanism of this action can be partly explained by the work of Soskin¹⁶

myalgia on the 28th day as a result of a toxic response to the administration of thiouracil, showed a rise of the basal metabolism rate from the initial +44 to +63%. The galactose index dropped from 190 to 135, indicating improvement

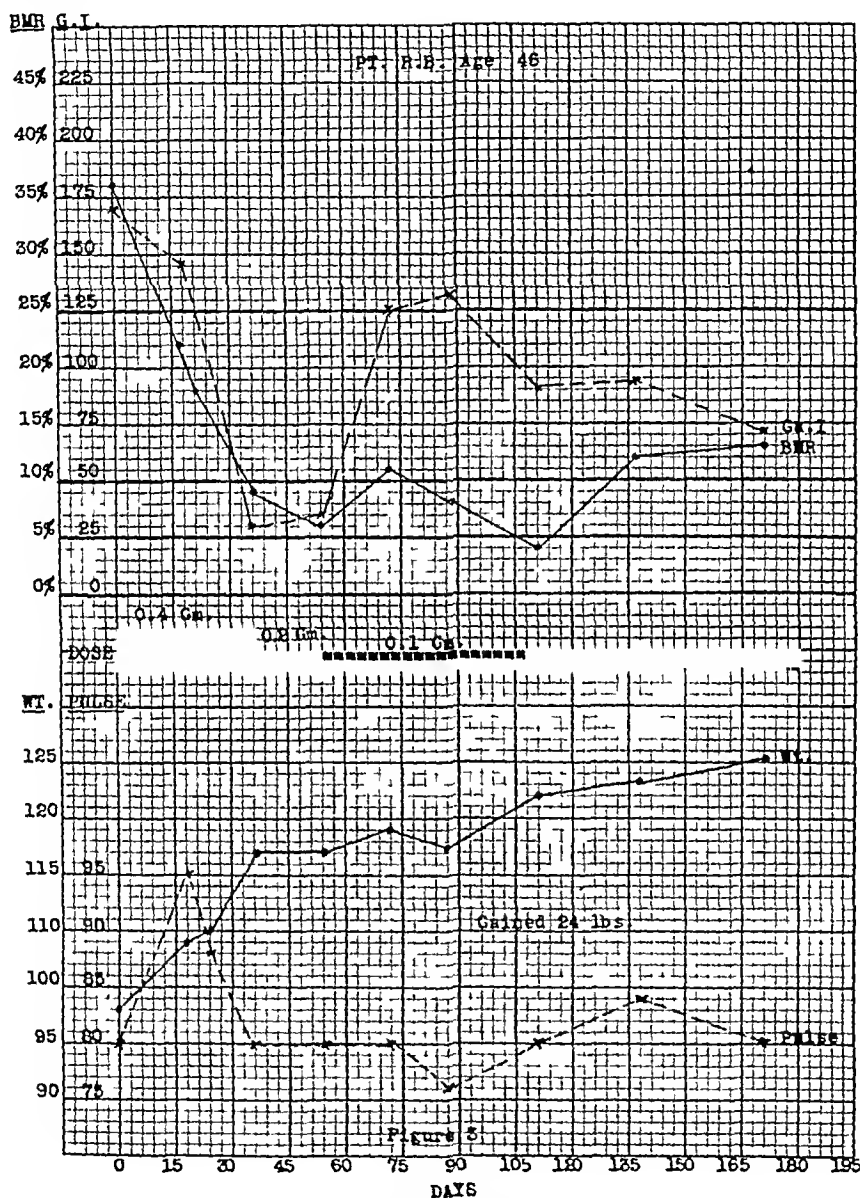


FIG. 3.—Galactose test showed more sensitive fluctuation to change in dose of thiouracil than did the basal metabolism rate.

who showed that thyroxin influenced the absorption of ingested carbohydrate. The factors, outside of the thyrotoxic state, that will increase the basal metabolism rate during treatment will not influence the galactose test. One patient, C. B. (Fig. 4), who developed pyrexia and

in the thyrotoxic state, notwithstanding the increased basal metabolism rate occasioned by the fever and muscle pain from which the patient was suffering.

Among the patients studied there were 6 that presented symptoms not clearly those of hyperthyroidism. Three of these

had had thyroidectomies and were referred to us because of the persistence of the symptoms after operation. All 6 patients had increased basal metabolism rates and consequently posed a difficult problem as to whether or not they represented

basal metabolism rate dropped. Reference to Table 2 shows that the drop in the basal rates was probably due to the reassurance of the patient. Neither the galactose test nor the cholesterol level showed any change in 5 of the 6 patients

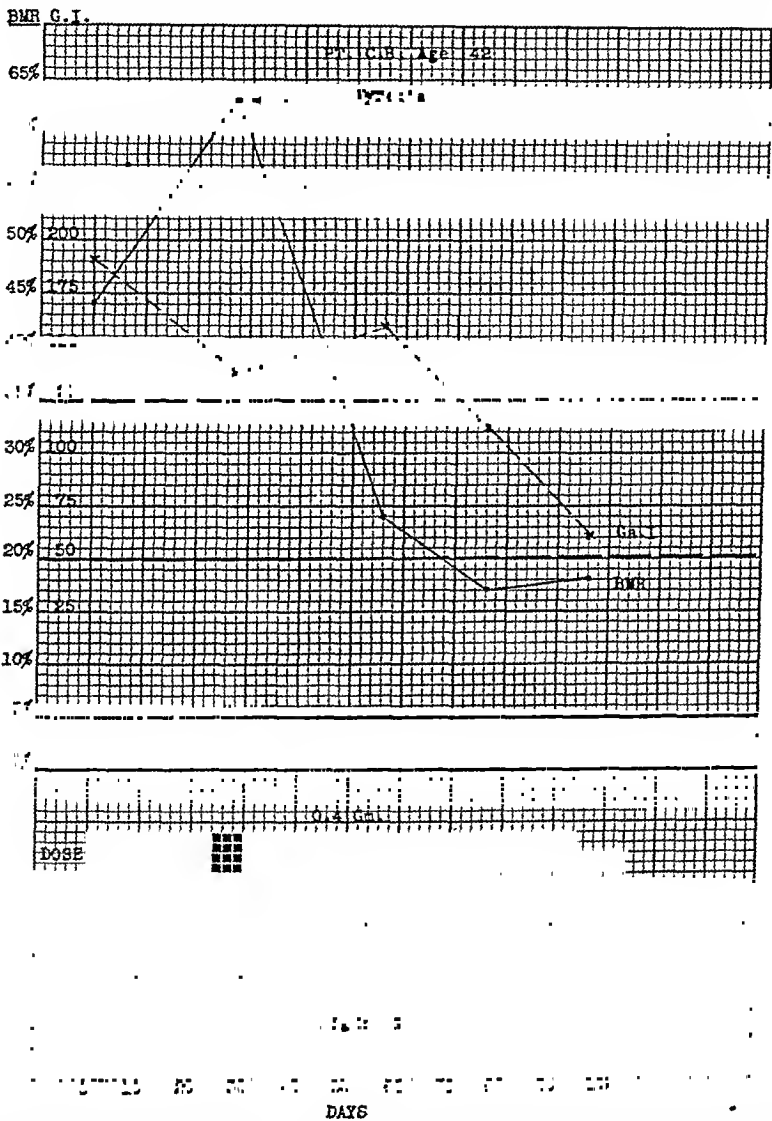


FIG. 4.—Some factors that influence the basal metabolism rate have no effect on the galactose test. Pyrexia, as a complication caused rise in the basal metabolism rate but did not influence galactose test.

true cases of thyrotoxicosis. The galactose index in some was increased and in others was normal. In 4 of these cases, after the administration of thiouracil for a period of 68 to 96 days, the galactose test did not vary appreciably, while the

recorded. Hypertension may have influenced the basal rate in 4 of the 6. Three patients had had thyroidectomies without alleviation of the symptoms. The reason for the high initial galactose index in 4 of these patients is not clear and represents

some of the 30% in whom the test is not in itself an aid to diagnosis. When it was employed in these patients as a diagnostic aid, after thiouracil was used as a therapeutic test, it proved helpful in determining the thyroid state of the patient.

Occasionally, the basal metabolism rate does not reflect the degree of improvement that is observed clinically. When such a patient is being prepared for operation it is reassuring to have other confirmatory laboratory evidence. The curves plotted in the case of Patient M. F. (Fig. 5) give evidence of this in a strikingly graphic manner. This patient was admitted in a state of cardiac decompensation associated with auricular fibrillation. The basal metabolism rate was +78% and the galac-

metabolism rate complement each other admirably. The latter observation is further evidenced in Table 3 in which 2 groups were chosen from the early studies in 1944. One group represented those cases that showed a recurrence of the thyrotoxic symptoms after operation, and the second group was made up of a small number of those that had not had any previous treatment. In some cases the basal metabolism rate was a better guide to treatment, while in others the galactose test was more informative. The recurrence of the thyrotoxic state after thyroidectomy does not imply that we are dealing with a type apart. The responses of the recurring and primary cases were alike.

TABLE 2

(The galactose index is a better therapeutic test when the basal metabolism rate is increased by causes other than hyperthyroidism.)

Name	Age	Sex	Basal metabolism rate		Galactose index		Cholesterol (mg. per 100 cc.)		Duration of therapy (days)	Comment
			Before	After	Before	After	Before	After		
M. L.	43	F	+31	+ 3	276	219	260	350	90	Prev. op.
C. W.	34	F	+15	+ 6	170	188	168	180	66	Prev. op.
I. R.	49	F	+29	+27	137	116	180	176	68	Prev. op.; B.P. 190/110
L. S.	50	F	+30	+ 5	104	70	266	232	83	Hyperten.; B.P. 240/130
C. T.	63	F	+37	+37	84	81	250	235	96	Hyperten.
C. J.	50	F	+28	+10	176	124	150	242	83	Hyperten.; B.P. 225/100

tose index was 440. At the end of 54 days of treatment with thiouracil, the basal metabolism was +50% and the galactose index was 180. The patient's intake of thiouracil was reduced to 0.2 gm. daily whereupon the basal metabolism rate rose to +58% while the galactose index dropped to 100. In the meantime the patient had gained 24 pounds in weight and the pulse had stabilized itself as to rate and regularity. The patient was subjected to an uneventful thyroidectomy. The converse of this case presented itself in which the galactose test was of no value in following the course of treatment and in which the clinical data supplemented by the basal metabolism rate were the criteria for subsequent treatment. The clinical condition of the patient still remains the *sine qua non* of treatment, while the galactose test and the basal

The use of the serum cholesterol determination as an aid to diagnosis and treatment had its shortcomings mainly in the fact that it was of no value in following treatment. As is generally known, the serum cholesterol is usually lowered in hyperthyroidism. Within 1 month after the use of thiouracil or propylthiouracil the serum cholesterol evidences a primary rise which is maintained throughout the course of the treatment regardless of the variations in the dose of the antithyroid drug. A composite chart of the laboratory data of 31 patients (Fig. 1) is shown which compares the responses as reflected by the 3 tests that were employed. The basal metabolism rate and the galactose index both showed a continuous decline for a period of 120 days, while the serum cholesterol showed a primary rise at the end of 30 days, which was then maintained

at approximately the same level for the entire course of treatment. After the primary rise, the cholesterol gave no indication of the therapeutic efficiency of the drug.

light of the work of Daft⁶ who employed crystalline folic acid to treat sulfa-induced granulopenia, and of Goldsmith and his associates⁷ who used "solubilized" liver as a source of folic acid to cure thiouracil-

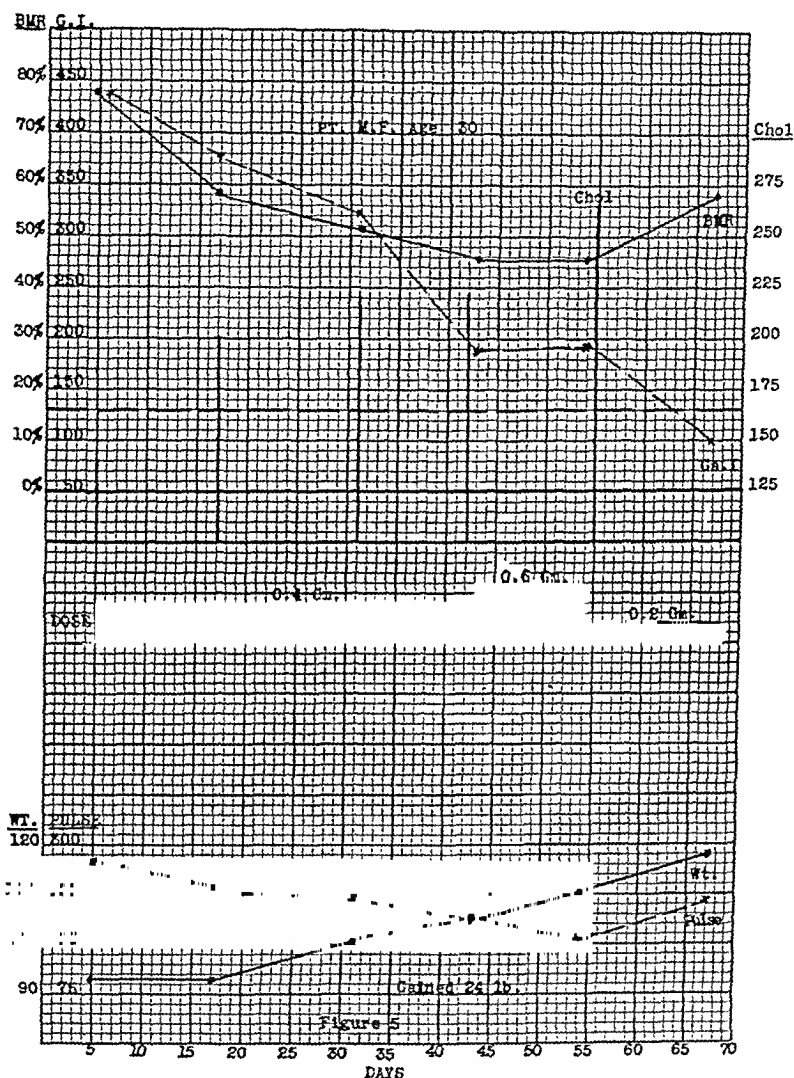


FIG. 5.—The galactose index reflected the clinical improvement, whereas the basal metabolism rate was not informative during treatment.

TOXIC EFFECTS. While the milder and less troublesome toxic effects of thiouracil are not a serious threat to its use, the depressive effect of this drug on the white blood cells and especially on the granulocytes is of paramount importance and emphasizes the care that should be exercised in the use of this preparation. In the

induced leukopenia and granulopenia in rats, we employed large doses of "solubilized" liver (5 capsules for each 0.1 gm.) in 40 patients for a period of 1 year. We do not believe that this influenced the effect of thiouracil on the blood pictures presented by the patients. One patient, who was being treated in this manner

(E. D.), developed granulopenia (21% neutrophils) 1 month after the onset of treatment. The total white count was 7000. This disparity between the white count and the granulocytes indicates the need for doing both the total and differential counts on all cases. The use of lactis casei factor (folie acid), intravenous pyridoxine and penicillin had no effect on the granulocytes as long as the thiouracil was continued. After the drug was discontinued, the differential blood count approached normal. Another patient (B. H.) was less fortunate. She repre-

to 18% in the 5 succeeding days. After vigorous treatment with penicillin the patient subsequently recovered. One patient (C. B.), who had exhibited an early toxic effect of pyrexia and myalgia 20 days after treatment was started, did well until 5 to 6 months later at which time she was on a very low maintenance dose of 0.1 gm. daily. At this time the white blood count and the granulocytes gradually declined so that the white blood count was 2350, with granulocytes 35%. The drug was stopped and the amount of "solubilized" liver administered was in-

TABLE 3

(Indicates that the basal metabolism test and the galactose test complement each other for purposes of diagnosis and treatment. Cases recurring after thyroidectomy are not different from primary thyrotoxic cases.)

Name	Age	Sex	Basal metabolism rate		Galactose index		Cholesterol (mg. per 100 cc.)		Duration of therapy (days)	Comment
			Before	After	Before	After	Before	After		
M. F.	30	F	+75	+58	428	102	140	266	67	G.I. better guide
E. M.	56	F	+75	+9	441	162	187	224	60	Died—apoplexy
D. A.	43	M	+36	-3	273	98	166	250	30	Prompt response
L. K.	39	F	+49	-2	176	56	176	163	63	BMR better guide
B. Sch.	44	M	+30	+1	117	73	188	228	56	BMR better guide
C. B.	42	F	+44	+18	191	61	145	190	66	Myalgia
L. H.	31	F	+19	-5	148	95	333	..	60	G.I. better guide
<i>Primary Thyrotoxic Patients</i>										
H. E.	58	M	+70	+27	181	145	171	200	46	Prep. for oper.
D. S.	42	M	+60	+29	234	134	184	240	40	Prompt response
A. T.	48	F	+55	-2	273	90	174	253	36	Prompt response
D. G.	32	F	+33	+4	143	129	222	200	45	BMR better guide
I. H.	26	F	+35	+1	153	60	39	G.I. better guide
B. S.	70	F	+42	+3	186	85	260	231	32	G.I. better guide
R. B.	46	F	+36	+13	172	72	190	222	42	G.I. better guide
M. S.	55	F	+61	+26	68	53	80	158	150	Diabetes present
F. A.	56	F	+16	0	228	89	320	307	41	Diabetes present

sented a case of malignant exophthalmos in whom there was a moderate degree of ophthalmoplegia. This patient was treated with thiouracil and a supplement of solubilized liver for 71 days. At this time she was on a daily maintenance dose of 0.1 gm. and 0.2 gm. on alternate days. In spite of this low maintenance dose the granulocytes dropped suddenly to 28% and the total white blood cells to 2050. Thionracil was discontinued and all reported methods of stimulating granulocytosis were instituted. In spite of this and several transfusions, the white blood count dropped to 950 and the granulocytes

increased to 32 capsules daily. The blood picture returned to normal after 10 days, which is enough time for spontaneous hemopoiesis to occur independent of any treatment. These specific cases are detailed in order to indicate that the size of the dose of the drug, the duration of treatment, and the prophylactic and supposedly curative effects of various preparations are neither safeguards nor means of therapy in the susceptible patient. These experiences emphasize the need for constant supervisory and follow-up examinations of the patients as long as they are

taking thiouracil, regardless of the dose or duration of treatment.

The less serious and transitory toxic effects in our cases consisted of pyrexia, myalgia, swollen submaxillary glands, peripheral edema and urticaria. The occurrence of the various toxic effects experienced by our patients is shown in Table 4. Of the 63 treated patients, 9 experienced 8 complications; 2 of the 9 patients experienced 2 types of toxic reactions. It is interesting to observe that the patient who developed agranulocytosis had experienced pyrexia as a complication one month previous to developing the agranulocytosis. The patient who experienced myalgia and pyrexia is 1 of the 2 who developed leukopenia several months later. This earlier susceptibility to the drug may

suffered from severe edema of the face associated with swelling of the submaxillary glands and edema of the glottis. This disappeared after emergency treatment. As a therapeutic test, 1 week after recovery, the patient was given $\frac{1}{2}$ tablet of thiouracil (0.05 gm.). Within several hours the patient's temperature rose to 103° F., her face and the soft tissues of the neck and throat became markedly edematous and she was in a desperate condition. One week after this toxic reaction subsided, propylthiouracil was substituted for thiouracil in a dose of 50 mg. 4 times daily. This was tolerated without any untoward effects and the clinical and laboratory response has been favorable. From present indications the use of propylthiouracil should supplant the use of thio-

TABLE 4.—COMPARATIVE INCIDENCE AND VARIETY OF COMPLICATIONS WITH THIOURACIL AND PROPYLTHIOURACIL

(Note the low incidence and the limited scope of complications with propylthiouracil.)

Complication	Thiouracil	Propylthiouracil
Pyrexia	3	0
Pyrexia + myalgia	1	0
Swollen submaxillary gland	2	0
Edema	1	0
Urticaria	0	3
Leukopenia	2	0
Granulopenia	1	0
Agranulocytosis	1	0
Total	11 (14.2%)	3 (8.1%)

be a means of cautioning the physician of a possible subsequent more serious complication. After subsidence of the mild complications, frequent observation of the patient, regularly repeated blood counts should be the rule.

We observed very little toxicity from the use of propylthiouracil in a period of 10 months. The only toxic effect as a result of its use occurred in 3 patients who later developed generalized urticaria. There was no depressing effect on the leukocytes or the granulocytes of any of the patients who were treated. In fact, 2 of the patients who developed leukopenia as a result of the use of thiouracil, when given propylthiouracil were able to tolerate it and experienced a return of their white blood count to normal. A third patient

uracil as the drug of choice in treating thyrotoxicosis.

THE PRE-SURGICAL AND THE MEDICAL TREATMENT OF THYROTOXICOSIS. The decision to employ non-surgical treatment in a case of thyrotoxicosis must be based on individual considerations of the case at hand. Those patients who are to be subjected to thyroidectomy follow an established pre-surgical routine. It has been our plan to prepare these patients with one of the anti-thyroid drugs until both the laboratory and clinical data indicate that the condition of the patient is at the optimum point. The average patient requires 3 to 4 months of ambulatory thiouracil treatment. An occasional individual case requires a longer period. After optimum conditions are achieved, the thio-

uracil or propylthiouracil is discontinued and Lugol's solution is administered for 18 to 21 days. The patient is then admitted to the hospital for thyroidectomy.

The purely medical treatment of thyrotoxicosis was reserved for those who had had 1 or more previous thyroidectomies and exhibited recurrences; for the aged who proved to be poor surgical risks; for patients with advanced cardiac failure; and for those who refused surgical treatment. Fifteen such patients were treated with thiouracil alone. Though the number is small, the duration of treatment and length of follow-up afforded us an opportunity to observe what may be expected

average period of approximately 15 months and of these, 3 have remained symptom-free for from 21 to 23 months. We must not consider these sustained remissions as cures. A much longer period of observation and the use of newer preparations may alter these conclusions. Tentatively, we can say that the anti-thyroid drugs precipitate a remission chemically in the same manner that surgery does mechanically: not by correcting a fundamental etiologic factor, but by producing a readjustment of the endocrine interrelationship. The incidence of recurrence (33%) in our series is lower than that reported by Williams,¹⁸ and by Rose and

TABLE 5

(Prolonged treatment with thiouracil lengthens the incidence [66%] and duration of remission in medically treated patients.)

Patient	Diagnosis	Thiouracil treated (mos.)	Relapsed after treat. (mos.)	Period of remission (mos.)
L. K.	Previous operation	9	12	
M. M.	" "	12	6	
D. A.	" "	9	..	21
A. C.	" "	10	..	7
R. C.	Diffuse, toxic	12	..	13
R. B.	" "	9	..	23
M. B.	" "	12	..	10
M. V.	" "	12	..	14
B. S.	" "	8	10	
M. S.	" "	8	..	23
A. T.	" "	12	..	19
M. W.	Toxic, nodular	11	7	
T. K.	" "	10	..	13
F. A.	" "	9	6	
A. A.	Exophthalmia	8	..	14

from this treatment. The therapeutic and maintenance doses were in keeping with our previously described procedure. Patients were arbitrarily treated from 8 to 12 months. The average length of treatment was 10 months. Reference to Table 5 will indicate the variety of cases. The type of goiter bore no relationship to the period of remission or incidence of relapse. Five patients experienced recurrence of symptoms after treatment was stopped. These occurred between 6 and 12 months after discontinuing the thiouracil. This represents an average of 8 months of freedom from symptoms before recurrence. Ten have shown no recurrence of the thyrotoxicosis for an

McConnell.¹⁴ The higher incidence of remissions (66%) is apparently due to the prolonged period of treatment. Though the incidence of remissions bears a direct relationship to the duration of treatment, it must be borne in mind that prolonged treatment also increases the probabilities of toxic reactions supervening. This was exemplified in 2 patients who developed leukopenia 5 to 6 months after the initiation of treatment. With the advent of less toxic preparations the criteria for the choice of patients to be treated medically may be modified to include a larger group because prolonged use of the drug may be employed with greater safety. Prolonged treatment may increase the duration of

the remission. Recourse to surgery can still be had for those medically treated patients who relapse into the thyrotoxic state after treatment has been discontinued.

The resumption of the use of thiouracil after the recurrence of symptoms did not interfere with its efficacy, nor did it preclude changing to propylthiouracil in any of our patients. Three patients were given propylthiouracil immediately after being controlled with thiouracil without any loss of effect of the drug, while 5 patients, whose symptoms had recurred after discontinuing thiouracil for a period of 6 to 12 months, responded favorably to treatment with propylthiouracil.

Discussion. The basal metabolism rate, the galactose thyroid function test, and the determination of the serum cholesterol were employed as diagnostic and therapeutic guides in 100 patients treated with thiouracil and propylthiouracil. The basal metabolism rate and the galactose test complemented each other in some cases both for diagnosis and treatment. The determination of the basal metabolism rate still remains the simplest and most desirable laboratory procedure. The galactose test is an excellent, and in some cases, a more informative supplement. The determination of the serum cholesterol alone affords practically no information regarding the improvement of the patient under treatment.

The prophylactic use of "solubilized" liver in conjunction with thiouracil did not prevent the occurrence of 1 case of agranulocytosis, 1 of granulopenia and 2 of leukopenia. The subsequent use of large doses of lactic casei factor (folic acid) and of intravenous injections of pyridoxine⁵ did not stimulate the granulocytes. The administration of 50,000 units of penicillin every 3 hours combated infection sufficiently long to allow spontaneous granulocytosis to occur in a case of agranulocytosis. The patients who developed toxic reactions to thiouracil were able to take propylthiouracil without ill-effects. The leukocyte count of the

patients with leukopenia returned to normal after this change of drugs. The only toxic effect that we observed with the use of propylthiouracil was the development of transient urticaria in 3 patients.

The markedly decreased toxic effects of propylthiouracil allow it to be employed for a longer period of time with comparative safety. The prolonged medical remission thus produced may be a factor in reducing the incidence of recurrence of symptoms after the drug is discontinued. The medical treatment should be reserved for patients with mild diffuse toxic goiter without exophthalmos and without too much enlargement of the thyroid, as well as for those who are not considered satisfactory surgical risks.

It should be emphasized that toxic nodular goiters should not be treated for a prolonged period of time in a desire to effect a sustained medical remission. The experimental work of Bielschowsky³ and the subsequent confirming work of Cantarow *et al.*⁴ indicated that the hyperplastic action of thiouracil on the thyroid gland in the presence of a carcinogenic agent such as 2-acetyl-amino-fluorene, caused localization of the carcinogenic effect in the hyperplastic gland. In the light of this work it would appear advisable to subject toxic nodular goiters that are prepared with thiouracil to subtotal thyroidectomy. The surgical treatment remains the treatment of choice. The mortality rate of 0.73% as reported by Lahey⁶ in the pre-thiouracil era has been reduced to 0.17% since the advent of the combined use of iodine with thiouracil. Because propylthiouracil offers more safety than thiouracil, its use in the pre-surgical preparation and in the medical treatment will be expanded. The progress of time will permit a more secure appraisal to be made of the remissions that are secured with the anti-thyroid drugs. In the meantime, we have at our disposal drugs, which when used judiciously and with vigilance, will decrease the period of hospitalization and the mortality rate in surgically treated patients.

Summary and Conclusions. 1. The clinical effects and the laboratory response to thiouracil and propylthiouracil were observed in 100 thyrotoxic patients over a period of almost 3 years.

2. The galactose thyroid function test was helpful as a therapeutic guide and as a diagnostic supplement to the basal metabolism rate in 70% of the patients.

3. The prophylactic use of "solubilized" liver as a source of folic acid failed to prevent the occurrence of 1 case of agranulocytosis, 1 case of granulopenia and 2 cases of leukopenia in thiouracil

treated patients. Neither the use of pyridoxine intravenously, nor large doses of folic acid stimulated granulocytosis.

4. Propylthiouracil is less toxic and more potent than thiouracil and apparently can be used with relative impunity in thiouracil-treated patients.

5. Ten of the 15 thyrotoxic patients treated medically with thiouracil showed a remission of from 7 to 23 months.

6. The pre-surgical preparation of thyrotoxic patients with the antithyroid drugs lessens the mortality rate and decreases the period of hospitalization.

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STUDIES OF BIOTIN METABOLISM IN MAN*

IV. STUDIES OF THE MECHANISM OF ABSORPTION OF BIOTIN AND THE EFFECT OF BIOTIN ADMINISTRATION ON A FEW CASES OF SEBORRHEA AND OTHER CONDITIONS

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BIOTIN remains one of the group of B vitamins that has not been responsible for clinical deficiencies in man. This could readily be explained by the fact that intestinal synthesis produces very adequate amounts of biotin, as was suggested in Part II of this series of papers.¹¹ Since that report was published in 1943, others^{3,4,5,9,10} have shown that almost all of the B vitamins are synthesized in the human colon. These include thiamine, folic acid, and others, the lack of which causes deficiency states. Thus it would seem possible that unusual circumstances might occur that would lead to a biotin deficiency. The facts that a normal constituent of the diet, namely raw egg white, interferes with biotin utilization, and that sulfa drugs inhibit bacterial growth in the colon, suggest possible ways to interfere with this protective mechanism. These facts have been utilized to produce biotin deficiency in animals. The present experiments were designed to study their significance in man. A search has also been made for evidence of states of biotin deficiency with the aid of a tolerance test and some suspected cases have been treated with biotin.

There have been 3 attempts to produce biotin deficiency in humans. In all of them, avidin in some form was used. The first reports were made in 1942 by Sydenstricker, Singal, Briggs, DeVaughn and Isbell.¹⁵ They used 7 human volunteers but were able to complete their experiments with only 4. The diet given was designed to be low in vitamin B members, though no estimates of its biotin

content were made. It contained 200 gm. of dehydrated egg white which was taken in solution in 3 equal portions with each meal. Usually the egg white furnished more than 30% of the total daily caloric intake. Changes were noted during the 3rd and 4th weeks when all subjects developed a fine scaly dermatitis. This cleared, but skin or mucous membrane changes developed later. After the 5th week mental or nervous symptoms resembling experimental thiamine deficiency developed. The urines at about this time showed a marked reduction of biotin content, from a normal of 29 to 62 μ g. per 24 hours to about 3.5 to 7. This rose rapidly after the injection of a biotin concentrate, about 150 μ g. of which were required daily for relief of symptoms.

The second report of an attempt to produce biotin deficiency in man was made by Rhoads and Abels in 1943.¹² This experiment was done with the hope that a biotin deficiency might delay the course of mammary carcinoma in 1 patient and of leukemia in another. Diets containing 46 to 60 μ g. of biotin were used and they were supplemented by raw frozen egg white, dried egg white and avidin concentrates. For the first 12 weeks, the equivalent of 1000 to 1200 units of avidin was used (1 unit of avidin inactivates 1 μ g. of biotin). This was later increased by 500 to 750 units for the next 16 weeks and finally by 1000 to 1250 units for the last 2 weeks. In spite of these large amounts of avidin, no decrease of the urinary ex-

* This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

cretion of biotin occurred* and no signs of deficiency disease simulating those described by Sydenstricker and his co-workers¹⁵ appeared.

Kaplan⁷ gave egg white or avidin concentrate to 10 patients with malignant disease. A general diet as free as possible from food rich in biotin was used, and was supplemented with from 36 to 42 egg whites per day. Later in the study, an avidin concentrate capable of inactivating 2000 μg . of biotin per day was used. Most of the patients were observed for many months, and none of them showed any signs of a biotin deficiency. Urinary excretion studies were not reported.

The failure of 2 of these 3 groups of workers to produce a biotin deficiency by administering large amounts of avidin is difficult to explain, and the discrepancy between the results is also confusing. Several possibilities suggest themselves. Avidin is a relatively insoluble material and it may not have been available for this reason in the experiments by Rhoads and Abels,¹² and by Kaplan.⁷ Since avidin is thought to prevent the absorption of biotin from the intestine, another explanation would be that the avidin-biotin complex is not stable in the human intestinal tract. All of the patients who could not be made biotin-deficient had malignant disease, and the possibility exists that they utilize biotin differently for this reason. Our first group of experiments was done to test these possibilities.

Methods and Results. A biotin tolerance test was devised. Twenty-four hour urines were collected from patients on an unrestricted diet, and after a control day, a dose of 500 μg . of biotin was given which caused a marked increase in urinary output above the normal. Several days after the first dose, the same quantity of biotin was given with 250 mg. of avidin, an amount which completely inactivated this much of biotin in the test-tube. The avidin was given in various ways. It was dissolved in ammonium sulfate, it was mixed with biotin in milk, and powdered biotin and avidin were

mixed and given in capsules. Four patients were used. Two of them had pernicious anemia, and were shown to have no free hydrochloric acid in their gastric contents. The other 2 patients had malignant disease. One had a bronchogenic carcinoma and the other had chronic myelogenous leukemia.

The results of these experiments are given in Table 1. They show that the avidin, by all methods of administration, effectively prevented the biotin from being excreted by all the patients and that avidin and biotin react in the human intestinal tract of patients with achlorhydria or malignant disease in the same way that they do in normal animals.

A study of biotin absorption from the colon was next made. Two subjects who had shown a striking increase in the urinary output of biotin after an oral test dose were given a dose by rectum. The biotin was dissolved in a few cc. of water. It caused an increase in the urinary output that was smaller than that which followed an oral dose, but large enough above the normal to indicate definite absorption (Table 2). The effect of sulfa drugs on the suppression of synthesis of biotin was also studied. We thought that a biotin tolerance test might indicate some degree of unsaturation in patients who had taken sulfa drugs for varying periods of time. In 6 normals, the amount excreted on the biotin day was 4 to 10 times that eliminated on the control day and varied from 245 to 337 μg . Two patients, 1 of whom took sulfadiazine for 2 weeks, and the other for 2 months, were tested. No evidence of biotin unsaturation could be demonstrated. A similar procedure was carried out on a patient who took sulfasuxadine in doses of 9 gm. per day for 16 days. His tolerance test showed a decidedly smaller output of biotin after the sulfasuxadine period than before, and suggested some degree of biotin unsaturation. However, his urinary output on the 16th day of sulfasuxadine was normal (Table 2).

* The method of biotin assay used measured both the true and the non-combinable biotin, described in Part III of this series.

Two other patients were studied with much more detail. They were kept on a diet free from liver, kidneys and sweet-breads but otherwise unrestricted. Such diets probably contain less than 65 μ g. of biotin per day.¹¹ With each meal they drank a glass of milk containing the whites of 2 raw eggs. This much raw egg

was saved. Every 4th night a dose of ear-mine was given which could be identified in the stools, and each 4 days' stool specimens were pooled, dried and analyzed for biotin according to the procedure previously described.¹¹ The results of the study on 1 patient are shown in Figure 1.

This patient, who was 46, had a hepa-

TABLE 1.—EFFECT OF BIOTIN AND BIOTIN PLUS AVIDIN ADMINISTRATION ON THE URINARY OUTPUT OF BIOTIN

Day	Biotin per 24 hrs. (μ g.)	Remarks
1	28	
2	140	500 μ g. of biotin in milk
3	23	
4	26	500 μ g. of biotin and 250 mg. of avidin in milk
5	25	
6	33	500 μ g. of biotin and 250 mg. of avidin in (NH ₄) ₂ SO ₄ in milk
7	24	
1	38	
2	237	500 μ g. of biotin in capsules
3	68	
4	88	500 μ g. of biotin and 250 mg. of avidin in capsules
5	30	
1	16	
2	19	
3	25	
4	211	500 μ g. of biotin in capsules
5	24	
6	20	
7	38	500 μ g. of biotin and 250 mg. avidin in milk
8	29	
9	25	
10	366	500 μ g. of biotin in capsules
11	60	
12	48	
1	14	
2	14	
3	15	
4	125	500 μ g. of biotin in capsules
5	24	
6	23	
7	21	500 μ g. of biotin and 250 mg. avidin in capsules
8	17	
9	21	
10	139	500 μ g. of biotin in capsules
11	31	
12	24	

white contains enough avidin to inactivate about 115 μ g. of biotin. In addition, they were given sulfasuxadine, sulfathalidine, or streptomycin by mouth to arrest bacterial growth and biotin synthesis in the colon. Since vitamin K is also synthesized by colonic bacteria, they were given oral vitamin K and their prothrombin times were followed. Each day's urine

toma of the liver. He ate poorly but took the milk and egg white faithfully. He was out of bed and his general condition remained fairly good until the day before the end of the experiment when he developed an interperitoneal hemorrhage from which he died. He showed a marked decrease of biotin synthesis in the stools and a fall of the urinary output to a low

level. There were no clinical signs suggestive of a biotin deficiency, possibly because the experiment did not last long enough.

A second patient was selected with the hope that he could be carried on the program long enough to be made deficient.

He was 63 and had chronic myelogenous leukemia, recently brought into remission by Roentgen ray therapy. He was not strong but was out of bed and ate fairly well. At first he was given 9 gm. of sulfasuxadine a day because 15 gm. had caused diarrhea in the other patient. On

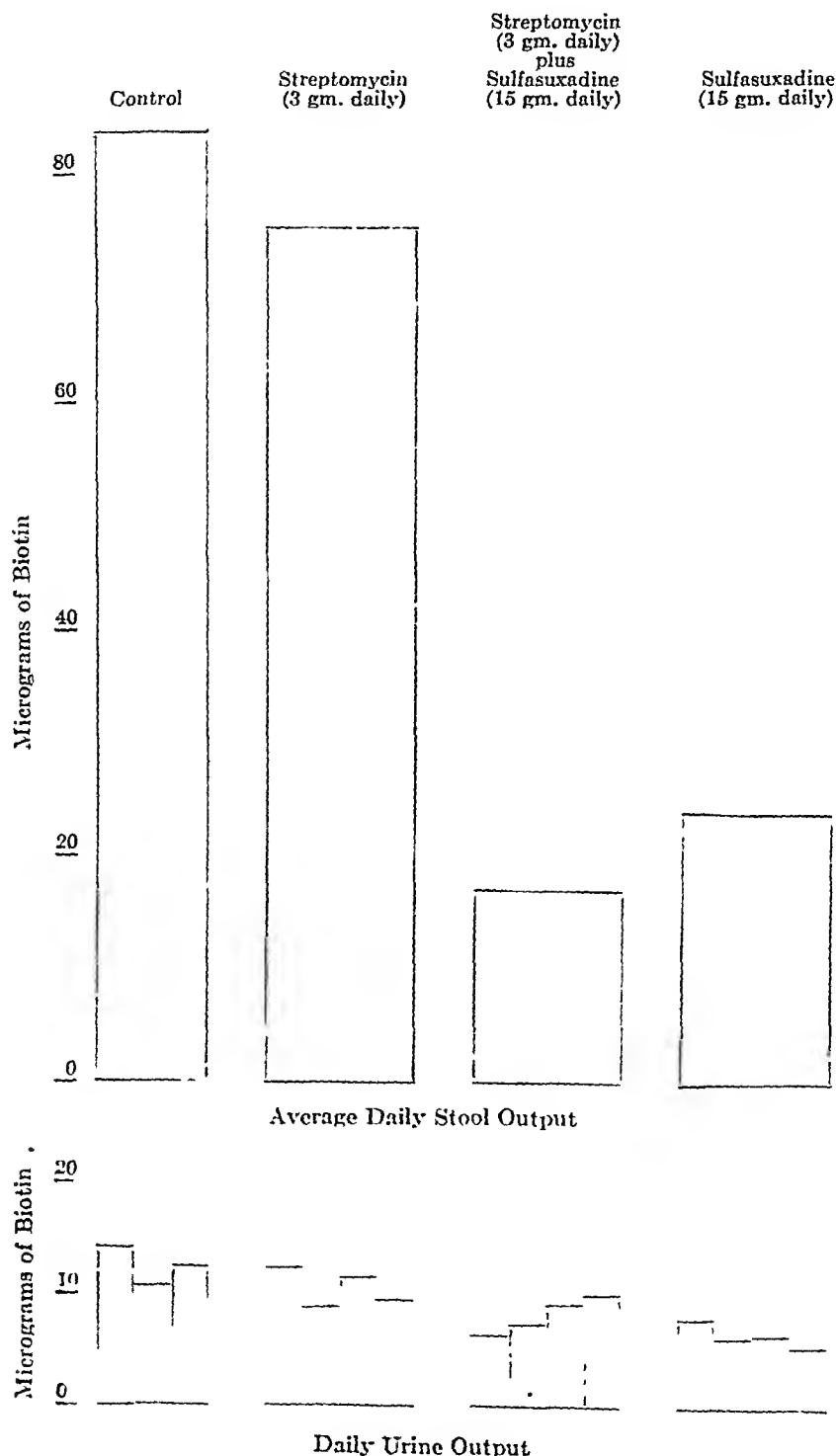


FIG. 1.—Effect of drugs on biotin synthesis.

the 5th and 6th days, his (undiluted) prothrombin time became prolonged (the diluted prothrombin time remained normal) and the sulfasuxadine was stopped and 3 mg. of vitamin K were given parenterally. Two days later, his prothrombin time was normal and 6 gm. of sulfa-

formation. The experiment was discontinued after 46 days. A tolerance test at this time showed a slightly lower value than the test done before the sulfa drug was given (Table 2).

While these metabolic studies were underway, another group of patients was

TABLE 2.—BIOTIN TOLERANCE TESTS

Diagnosis	Urinary output of biotin (μg.)			Remarks
	Day of test:	1 (500 μg. of biotin)	2 3	
Normal	25	245	62	
"	78	337	71	
"	44	259	66	
"	42	311	46	
"	29	294	75	
"	38	303	74	
A.S. heart disease	57	244	53	
" " "		104*	54	* 1 mg. biotin by rectum
	42	263	62	
Bacterial endocarditis	34	148	58	Before sulfasuxadine
	43	95	41	After 16 days of sulfasuxadine
" "	46	416	138	After 2 weeks of sulfadiazine
	59	113*	69	* 500 μg. biotin by rectum
Lung abscess	64	378	64	After 8 weeks of sulfadiazine
Cirrhosis	45	407	92	
"	24	208	84	
"	56	293	106	
Peptic ulcer	23	232	79	
" "	54	279		
Neoplasm	17	203	41	
"	10	124*	18	* Incomplete specimen
"	28	140	23	
Leukemia	40	168	24	Before sulfa drugs
"	15	125	24	After 46 days of sulfasuxadine and sulfathalidine
Seborrheic dermatitis	39	132	123*	* After 20 days 250 μg. biotin daily
" "	15	119	157*	* After 14 days 250 μg. biotin daily
"	15	114	180*	* After 29 days 250 μg. biotin daily
"	10	156	342*	* After 20 days 250 μg. biotin daily
"	52	231	120*	* After 13 days 250 μg. biotin daily
Atopic dermatitis	41	153	34	
Alopecia totalis	24	258	286*	* After 19 days 250 μg. biotin daily
Alopecia areata	40	52		
Myotonia congenita	33	233	50	517* * After 7 days 1 mg. biotin subcutaneously daily
Aplastic anemia	49	244	50	
Pernicious anemia	38	239	68	
"	25	211	24	
"	82	352	209*	* After 19 days 250 μg. biotin daily
Non-tropical sprue	31	331	25	

thalidide was begun. This was later increased to 8, 10 and finally 12 gm. a day. The patient had no diarrhea, his appetite and strength improved and he gained weight. There were no clinical signs of a deficiency state and his stool and urine analysis showed no decrease of biotin

observed for evidence of biotin deficiency. For the past 15 or more years various workers have suggested that certain disease states may be due to a lack of biotin (vitamin H), but the first report of a clinical case was made by Williams¹⁶ in 1943. His patient, a 66 year old man with

eccentric dietary habits, had consumed 2 to 6 dozen raw eggs per week as part of an otherwise poor diet which included large amounts of wine. When admitted to the hospital, his entire face, ears, shoulders, dorsum of the forearms, hands and lower legs were fiery red and covered with medium sized scales. On the ward diet, the rash promptly cleared and it did not return when egg white and a low biotin diet were later given. The next report of human biotin deficiency was made during the last year by Chavarria² and co-workers from Costa Rica. They observed that children with vitamin B deficiency of severe degree developed canities and alopecia which disappeared when the other manifestations of the deficiency state were cured by a good diet. They thought that the addition of 0.25 mg. of biotin 3 times a day accelerated the return of the hair to normal.

Our studies were made principally of patients who might be expected to have evidence of vitamin B deficiency or who had skin or hair changes resembling those in biotin-deficient animals. Biotin deficiency has now been produced in the chicken, duck, rat, mouse, hamster, rabbit, dog, pig, calf and monkey, and the picture is quite similar in all of them. It is mainly a loss of hair (or feathers), a seborrheic type of skin rash and, in the late stages, the development of a sudden and severe paralysis. The latter has been shown to respond to potassium administration and resembles periodic family paralysis.^{13,14} There have been no lesions in the central nervous system.

We used the following program in our study of patients. A biotin tolerance test was done to look for evidence of low biotin excretion in the urine or biotin unsaturation of the tissues. In some instances, a stool was analyzed to see if biotin was being synthesized. To several patients, 250 μ g. of biotin a day was given for 4 to 8 weeks to see if it would improve the clinical condition. On these patients, a 24 hour urine was examined 1 week or 2 after therapy began to see if the biotin

was being utilized or excreted in the urine. The results seemed to indicate in every instance that the dose was adequate. In a few instances larger doses were administered but the test always showed that about half of the biotin administered was eliminated in the urine. The results of these procedures are shown in Table 2.

Most of the patients responded to the tolerance test in the same way as the normals, excreting about half the test dose or more. A few patients excreted relatively small amounts after a test dose which may indicate that their tissues were unsaturated. It is of considerable interest that 4 of the 5 patients with seborrhea had low values, excreting less than a third of the test dose. These patients all received biotin daily for 1 month or more with the following results. The first patient had seborrhea and mild dermatitis of the scalp which seemed to improve in about 1 week and did not recur for several months. The second patient had an extensive dermatitis of the face and scalp. This showed slight improvement for 1 month, after which it relapsed while under treatment. The third patient had a mild dermatitis on many areas of the body and developed an acute generalized dermatitis from the overzealous use of local remedies. While this reaction was subsiding, he was given biotin and only bland local therapy on which he did well. When the skin was healed, he still had a very oily skin on the face and scalp. The fourth patient had seborrhea of the scalp and a dermatitis in the interscapular regions. Neither condition changed under therapy. The fifth patient had a classical seborrhea of the scalp with dermatitis at the hair-line, ears and nasolabial fold. It did not improve in 4 weeks of treatment. In addition to the 5 patients with seborrhea, biotin was also given to 2 patients with alopecia areata and 1 with atopic dermatitis without beneficial effect. They also received 250 μ g. daily for 1 to 2 months. Stools were analyzed on most of these skin patients and all were found to have biotin in normal concentration.

In view of the report from Costa Rica,² we were very hopeful that a patient with pernicious anemia and premature white hair would benefit from biotin administration. She was 39 years old and had been studied at this hospital for 20 years. At the beginning of her illness, the diagnosis was not clear, but later it was found that she could be kept in good general health and a normal blood count could be maintained by large doses of liver or folic acid. Neither of these treatments had affected her gray hair. This began shortly after the onset of her anemia and had progressed gradually until it became marked. All of the hair on her body had become smaller in diameter and had completely lost its pigment. It had been that way for 5 years when our experiment was made. She showed biotin present in the stool and a normal urinary excretion and response to a tolerance test. After 19 days of 250 μ g. of biotin a day, she eliminated 209 μ g. of her daily dose, a result which seemed to indicate quite a high degree of saturation of the body with biotin. Two months of biotin therapy had no definite effect on the canities. There had been no hair loss and no new hair grew. There have been reports that patients with pernicious anemia are deficient in several of the B vitamins by chemical test.¹ Our 2 other patients with pernicious anemia and 1 with non-tropical sprue showed a normal response to the biotin tolerance test.

In the third paper of this series,¹¹ it was shown that 2 biotin-like materials are excreted in human urine. One combined with avidin and thus reacted like true biotin. The other failed to combine with avidin and it was suggested that it might be a breakdown product of biotin which was excreted in the urine. The urinary excretion of this non-combinable material was measured throughout all these experiments. It showed no variations that could in any way be related to variations of biotin intake or urine value. The biotin values of 15 urines were measured by *S. cerevisiae* plus avidin and *L. casei* methods.

Values for true biotin were the same by both methods but there was no non-combinable material in urine when measured by the *L. casei* assay. These findings do not support the idea that non-combinable biotin is a metabolic product of biotin.

Discussion. The theoretical problem involved in producing a biotin deficiency in man with avidin seems to be to prevent the absorption from the human intestinal tract of about 50 μ g. of biotin a day from food and several times that amount formed by intestinal synthesis. Nearly complete fixation of the biotin is probably necessary, since the daily minimal requirement is doubtless satisfied by only part of this amount. Avidin in sufficient quantity to combine with 1000 to 2000 μ g. of biotin did not accomplish this fixation in either the experiments of Rhoads and Abels¹² or those of Kaplan.⁷ According to the calculations, they gave more avidin than Sydenstricker and his associates,¹⁵ which makes it apparent that the problem is not based on avidin dosage only. The relative ratios of biotin to avidin in these experiments cannot be calculated, since the biotin content of all the diets is not known and it is possible that this ratio and other factors, such as the form in which biotin is given,⁶ are also important. Our experiments show that avidin inhibits the use of biotin by man and animals in the same way and there is nothing so far to indicate that the production of a biotin deficiency in man with avidin is not primarily a problem of using proper quantities and ratios.

In our experiments with sulfa drugs, ordinary dosages have not seriously impaired biotin synthesis. The type of drug and factor of dosage are important, and large doses of sulfasuxadine almost completely stopped biotin synthesis in 1 subject's colon. The 20 μ g a day he was eliminating in the feces are partly accounted for by the biotin contained in the 6 egg whites and in the food biotin which was fixed by the avidin in the egg whites. It would thus seem that synthesis was almost completely stopped. Whether

this inhibiting action of non-absorbable sulfa drugs can be maintained long enough to produce a biotin deficiency state in man, remains to be seen. It has been done in animals in less than 6 weeks.⁸ More work is needed to see how much harm can result from the inhibition of vitamin synthesis in man by sulfa drugs.

The study of patients with the aid of a tolerance test showed a low response by 4 of the 5 with seborrhea. This finding lends support to the idea, which has been proposed by several workers, that human seborrhea is related to biotin deficiency. Treatment of these patients with biotin has shown no consistent evidence that the treatment was of value. In a few other conditions with skin and hair disturbances, biotin has also failed to have any definite effect. No harmful effect of biotin administration for several months has been observed, and the results of urine output studies indicate that larger doses of biotin probably would not have done more good. The results thus do not indicate that any of the conditions studied are related to a lack of biotin.

The technical assistance of Mrs. Marion Goldberg Laeger is gratefully acknowledged. Supplies of biotin and avidin were kindly furnished by Dr. Elmer L. Severinghaus, Director of Clinical Research of Hoffmann-La Roche, Inc., Nutley, N. J.

Summary and Conclusions. 1. An oral dose of 500 μ g. of biotin given to human subjects as a tolerance test caused a marked increase in 24 hour urine output. In a group of normals, this varied from 245 to 337 μ g. The same dose given with 250 μ g. of avidin caused no increase of urinary output. Biotin given by rectum caused an increased urinary output.

2. Sulfa drugs in ordinary doses did not seriously interfere with the synthesis of biotin by bacteria in the colon, but large doses of sulfasuxadine caused almost complete inhibition of biotin synthesis.

3. A tolerance test showed that 4 out of 5 patients with seborrhea had a low urinary output after a test dose. Biotin administration to these and to a few other patients with skin disorders had no definitely beneficial effect.

4. Marked variations in the urinary output of biotin were associated with no consistent change in the urinary output of non-combinable biotin-like material. The urine values for biotin in assays done with *S. cerevisiae* and *L. casei* were the same. With *L. casei*, no non-avidin combining material was found.

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PENICILLIN THERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS

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AFTER the bacterial nature of this disease was demonstrated, there followed countless efforts to effect a "cure" by sterilization of the blood stream. It seemed, however, that the very character of the local endocardial focus defeated the therapeutic efforts. Masses of bacteria multiplying within a dense network of fibrin and blood cells and slowly destroying the valve are the essential pathologic lesion. A considerable list of various substances for oral, subcutaneous or intravenous administration were tried. Hexamethylenamine, quinine, salicylate, aniline dyes and various preparations of silver, mercury and arsenic all proved to be clinical failures.^{53,54} A review of the recorded cases reveals that the disease may end in apparent recovery but this is rare.²⁹

With the advent of the sulfonamides, new hope was given to the problem. Sulfanilamide,⁵¹ sulfathiazole and sulfadiazine were given clinical trials¹⁶ resulting in the adoption of sulfadiazine as the drug of choice. Attempting to break down the endocardial vegetations to reach the organisms, massive doses of sulfadiazine, intravenously and by mouth, were given. This therapy produced a blood concentration of from 40 to 85 mg. per 100 cc. of blood.⁵³ Untoward results, renal, gastric and on the blood, were consistently present. Because of these dangers and the variability of the results, sulfonamide therapy alone was concluded to be largely a therapeutic failure^{29,32,51} (see below).

Anticoagulants were introduced for the solution and prevention of the thrombovegetative lesions. Heparin was the drug advocated and after many applications, efficient and conscientious efforts proved heparin to be a clinical disappointment. The antibiotics, chiefly penicillin, opened

a promising field of therapy. Penicillin and heparin were administered together with varying results. It has been clinically shown that the cases which responded successfully were due to penicillin alone. The use of heparin or any anticoagulant has lost favor in the treatment of subacute bacterial endocarditis.^{28,31,42,52}

In the last 5 years reports have been slowly coming in stating the efficacy of penicillin. A sizable literature has accumulated and the prognosis of a previous uniformly fatal disease has changed. It is the purpose of this paper to correlate the facts obtained and review a large number of cases so that adequate conclusions may be made. This paper reviews 521 cases recorded in the literature all treated with penicillin. A careful analysis will attempt to elucidate a scheme regarding the dosage, route of administration and proper duration of therapy.

SUSCEPTIBILITY OF THE ORGANISM. All organisms isolated from the blood must be tested for their susceptibility to the type of penicillin which will be administered. This rule must be followed without exception.^{7,21,29,52}

Not infrequently a patient suffering with this disease is started on relatively small doses of penicillin before a positive blood culture is obtained. This practice is decidedly detrimental to the prognosis of the case. The organism may lose its sensitivity to penicillin, while the chances of obtaining a positive blood culture are lessened in spite of the addition of penicillinase to the culture material. Undoubtedly the endocarditis progresses and further embarrasses the heart. Nevertheless, it is best to withhold penicillin until a positive culture is obtained.

Fourteen patients presented overwhelmingly positive clinical signs and symptoms,

though repeated blood cultures failed to reveal a causative organism. Massive doses of penicillin were instituted and subsequent blood examination during therapy revealed organisms sensitive to penicillin. This method is too hazardous to the patient and is not recommended, although a clinical cure may be effected. If the routine methods fail to demonstrate a bacterial etiology, then anaërobic and arterial cultures should be tried.

The routine test tube serial dilution method or a modification of the Hobby²⁵ method was used to determine *in vitro* sensitivity. In 469 cases (90.1%) of the series, the *Streptococcus viridans* was the infecting organism. This organism exhibited an average range of sensitivity, *in vitro*, of 0.01 to 1 unit per cc. Of these 469 patients, 448 (95.5%) were considered as penicillin sensitive within therapeutic limits. The remaining 4.5% were therapeutic failures due to (1) relatively high resistance of the organism, (2) mixture of organisms, (3) hidden foci of infection containing resistant strains. Non-hemolytic streptococci constituted 6.2% of the cases, β -hemolytic streptococci 1.9% and all others 1.8%. These last mentioned organisms composed those cases which were regarded as penicillin resistant, with an average range of sensitivity of 0.9 to 6 and higher units per cc.

A possible source of error in the above figures may be due to the fact that since the *Strep. viridans* group is far more sensitive to penicillin than the others, it affords a ready clinical success. It is quite natural to report the successes rather than the failures. However, a careful survey of consecutive cases treated substantiate the overwhelming preponderance of this organism as the infecting agent. We may say then, that the common finding in this disease is a penicillin susceptible strain of *Strep. viridans*.

Priest³¹ *et al.* claim that *in vitro* sensitivity is not *per se* significant as regards ultimate success of therapy. Previous duration of the disease and adequacy of dosage are more important prognostically.

Christie⁷ in his excellent paper points out that the resistance of the infecting organism by ordinary methods appeared to be of no clinical importance within a wide range. Only when the organism was more than 10 times as resistant as the standard test staphylococcus did this measurement appear to be of therapeutic and prognostic significance.

Let the reader be aware that it is the determination of sensitivity to penicillin that guides the dosage and duration of therapy. Repeated tests made during the course of treatment indicate if sterilization, increased or decreased sensitivity is being effected. Some will argue that massive doses, enough to overwhelm any organism regardless of its degree of sensitivity, obviate the need of these tests. Obviously successes will be achieved, for as pointed out the great majority of cases are sensitive. This type of "pseudotherapy" is frowned upon. It is to be hoped that physicians will not reach for their penicillin somewhat as a panacea. Stressing this point, Reimann⁴⁴ warns that 80% of penicillin now given is wasted because (1) fever is often the *only* indication for its use, (2) the dosage is too small, too interrupted, too large or is given longer than needed, (3) most important of all, widespread use of penicillin will gradually induce penicillin resistant bacteria which will cancel its curative effect.

Loewe³⁴ has demonstrated a special type of organism which he calls "*Streptococcus s.b.c.*"; it is for all purposes refractory to penicillin. Priest and McGee⁴⁰ isolated *Hemophilus parainfluenzæ* once in 4 refractory cases. The organism was not affected by penicillin *in vitro*, regardless of concentration. Examination revealed a sensitivity of the resistant streptococci to streptomycin of from 0.1 to 1 unit per cc. Streptomycin therapy was instituted with success. These organisms are not isolated with any frequency.

The unique work of Dick and Schwartz¹⁰ in producing experimental endocarditis in dogs by repeated injection of organisms isolated from human cases may be of

interest to the reader in view of the above discussion.

DOSAGE AND DURATION OF PENICILLIN THERAPY. Before discussing the dosage of penicillin a brief summary regarding the source of the organisms is in order.

Katz,^{28,29} Priest,^{41,42} Annone,² Ward⁵⁵ and others have conclusively demonstrated that infections of the upper respiratory tract, extraction of teeth, tonsillectomy and other minor ailments were the predisposing causes in over 70% of the cases. In this paper 408 cases (78.4%) resulted from the above causes. The logical solution of the problem of bacterial endocarditis lies in the prompt and adequate therapy of all known bacteremias, plus the prophylactic use of penicillin in extraction of teeth and in every case of upper respiratory infection or any other infection in patients suspected of having valvular involvement. Ideally, cultures should be made on all patients where a bacteremia occurs due to infection particularly in patients known to have cardiac damage. This led the Philadelphia Heart Association⁴³ to state, "All persons suffering from rheumatic fever should receive penicillin before all operations on the upper respiratory tract."

Thill and Meyer,⁵² in their recent work, have clearly demonstrated that penicillin therapy must be maintained for at least 3 days after the removal of a focus of infection if subacute bacterial endocarditis is to be prevented from developing in cases of known and suspected cardiac damage.

The close relationship between rheumatic fever and subacute bacterial endocarditis is well known^{5,48} since a previously damaged valve predisposes to bacterial invasion. Rheumatic fever was present in 65% of the case histories in this series.

Sulfamenazine^c has recently been used in rheumatic patients requiring teeth extraction as a prophylactic measure to combat any bacteremia which may further damage the heart. This drug, because of its low renal toxicity has been used in

patients requiring oral surgery during the course of penicillin treatment.

Before administering penicillin, all foci of infection should be looked for, especially oral sepsis. Eradication of these foci is essential if an adequate regimen of therapy is to be carried out.^{33,37}

A blood penicillin level of concentration to overwhelm the organism must be maintained at all times. This necessarily means a large daily dose of penicillin. What constitutes an adequate dose? Many workers^{21,54} have shown that a serum penicillin level of from 3 to 10 times the *in vitro* sensitivity of the organism is desirable. Why is this necessary? It was not completely understood²⁹ why some cases with sensitive organisms require only 2 weeks or less of treatment while others infected with organisms of the same degree of sensitivity require 6 to 8 weeks or more. Also, a wide variation of serum penicillin levels was obtained in different patients from the same dose by whatever methods given. Priest⁴¹ produced no cure in cases where the mean penicillin serum level was not above 0.5 unit per cc. and yet only 25% required more than 0.1 unit per cc. for *in vitro* inhibition.

A possible solution suggested is that as long as the organisms could multiply within and on the endocardial vegetations and serve as an active focus, therapy was useless. True, the peripheral blood from which cultures were made proved to be negative, but the moment the low dosage of penicillin was stopped, the cultures again became positive.⁴ Therefore the penicillin must penetrate deeply through a dense meshwork of fibrin to attack the clumps of bacteria. Because of the very nature of this lesion Levine⁵² admitted that "bactericidal agents cannot penetrate the fibrin and tissue that surround the causative organisms." "Merely sterilization of the blood stream is not sufficient for a cure." Nathanson *et al.*,³⁹ in expertly controlled experiments, reveal the heretofore assumed fact that penicillin can and does diffuse through fibrin. It can therefore be assumed that a definite low-

ering of the penicillin concentration in the blood is effected during penetration.

The experiments were performed on *B. subtilis* organisms, using penicillin assay cups. Human fibrinogen obtained from the Harvard Medical Research laboratories was used.

TABLE 1.—EFFECT OF SULFATHIAZOLE AND SULFADIAZINE ON *B. SUBTILIS* CULTURES IN FIBRIN

Diameter of Zones of Inhibition in millimeters			
Hours	Sulfathiazole	Sulfadiazine*	
24	0	0	
48	0	0	
72	0	0	
92	0	0	
120	0	0	

* M/25 concentration.

Table 1 reveals that there is no evidence of penetration of sulfathiazole and sulfadiazine into fibrin.

TABLE 2.—EFFECT OF PENICILLIN ON *B. SUBTILIS* CULTURES IN FIBRIN

Diameter of Zones of Inhibition in Millimeters				
Penicillin units/cc. 0.5		1	2	4
Hours				
24	9	9	9	10
48	9	9	9 5	12
72	9	10	10	12
96	10	12	13	14
120	10	12	14	
144	10	12	14	
168	10	12	14	

Results indicate that penicillin diffuses freely into fibrin as compared to sulfa compounds. It is clear, in evaluating the efficiency of a drug in the treatment of subacute bacterial endocarditis, that the ability to penetrate fibrin requires important consideration.

In the early days of the disease, the vegetations are small and the fibrin component is relatively sparse. As the disease progresses the fibrin is deposited with increased intensity and ulceration with final destruction of the valve may be the end-result.^{5,45} Thus, the period between onset and treatment of the endocarditis becomes vital to the patient. If penicillin is administered in the early stages, penetration is easier; therefore, the dose needed is small and the duration of therapy less-

ened. Priest⁴¹ and others^{12,36} conclude that if the duration of the disease without treatment is greater than 9 to 14 days, therapy must be intensified in proportion to the number of days without medication. By intensified treatment we no longer mean only increased dosage but prolonged therapy.

TABLE 3.—EFFECTIVENESS OF PENICILLIN IN RELATION TO DURATION OF DISEASE

Organism: *Strep. viridans*; average sensitivity: 0.05 unit/cc.

No. cases	Daily dose (units)	Duration (days)	Clinical cure (%)
30	100-200,000	14-21	56.1
18	100-200,000	28-40	64.3
22	300-500,000	14-21	72.8
46	300-500,000	28-35	87.5

Table 3 adequately explains the need of high dosage and increased duration to achieve better clinical results. None of these patients had received previous therapy. Thill,⁵² Rykert,⁴⁶ and others^{7,9,29} in their studies caution that patients who had received distinctly inadequate penicillin therapy before coming under observation presented a more difficult problem, as far as control was concerned. Increased bacterial resistance and progressive endocardial lesions were the essential factors in producing this problem. At present our methods cannot tell us the state of the vegetative lesions. There are no definite laboratory or clinical criteria available for predicting in which cases the disease will remain permanently cured after treatment is stopped and in which cases there will be relapses.

Another important reason for prolonged therapy is the matter of relapses (bacteremia). Experience teaches that if relapses occur they do so within the first 4 to 6 weeks of treatment. Relapses after 50 days are extremely rare. Regardless of penicillin concentration, the bacteria within the vegetations are very refractory.

Therefore, on the basis of the lesions and the clinical evidence the following plan is advocated: (1) daily dose of 500,000 units is given for a minimum of 28 days; (2) if at the end of this time the

patient is not doing well, the dose is increased to 1,000,000 units per day for another month; (3) penicillin serum levels are determined twice weekly.

At first glance this plan may seem radical, but a knowledge of the nature of the lesion, which progresses to destroy the valve, and of the materials used in treatment, demonstrates this time-dose relationship to be adequate. The reader is again reminded that clinically, increased dosage is no substitute for prolonged treatment. Delay in controlling the infection also exposes the patient to the many dangerous complications of this disease (see below).

ROUTE OF ADMINISTRATION. Agreed that treatment must last at least 1 month, the next point to decide is a suitable method of administering the penicillin. The method should be one which insures a more or less constant high effective level of penicillin in the blood stream. Penicillin is rapidly excreted. Intravenous, intramuscular or subcutaneous routes are the desirable modes of administration.

The frequency distribution of plasma penicillin levels at $\frac{1}{2}$ hour, $2\frac{1}{2}$ hours, and 3 hours after intramuscular injections of 10,000, 15,000 and 20,000 units were carefully studied.²⁵ At the end of 30 minutes, the level was maximum in relation to the dose and dropped rapidly until it was 0 unit per cc. The zero level was reached in 3 hours with 10,000 units, $3\frac{1}{2}$ hours with 15,000 units and 20,000 units. In order to maintain plasma levels of 0.5 unit per cc. or higher by intramuscular administration; continuous infusion or intermittent injection of penicillin around the clock must be used. While occasional cases have responded to intramuscular penicillin, given every 3 hours,^{30,55} this scheme is not advocated. For practical purposes, no drug remains after 2 hours from a single injection. If a uniformly high effective level is to be maintained by intermittent therapy, penicillin should be given every hour on the hour day and night for the entire treatment period in the great majority of patients. The total

24 hour dose is divided into 24 equal parts each dissolved in 1 cc. of sterile physiologic saline and injected into the gluteal region. Properly executed, this procedure is painless when purified penicillin is employed.

However, it is less wasteful of penicillin if the muscular route is used, to give the penicillin by continuous intramuscular infusion.¹² More advantageous is the continuous intravenous drip. Continuous intravenous drip is the route of choice, since penicillin enters the circulation directly and affords a faster control of the disease. Patients with mild congestive failure can tolerate the extra fluid if the sodium intake is low.¹⁴ The penicillin is dissolved either in physiologic saline or 5% glucose. Thrombophlebitis is the only complication of prolonged injection of a vein, therefore the site of administration is often changed during therapy.⁴¹

The administration of penicillin in peanut oil and beeswax¹⁸ to several cases has produced good results after a single daily injection of 300,000 units. This method has its limitations, for the patient must be watched, and laboratory procedures prevent his being "ambulatory." At present this method is receiving further study with the more purified penicillin products.

With the recent advent of highly purified penicillin, subcutaneous administration has come to be of practical importance. Experimental studies reveal an adequate blood level after subcutaneous injection equal to intramuscular injection. To date this method has not been used. Foter *et al.*²⁰ suggest that rubber tubing intended for continuous drips procedures be checked for inactivating effects, for their experiments confirm reports from England on the inactivating effect of synthetic rubber upon solutions of penicillin. Clinically, this inactivating effect has not as yet been noticed. The preparations of penicillin used in this study were: (1) an almost pure amorphous sodium penicillin (1550 units per mg.) put up in 200,000 unit vials; (2) crystalline sodium

penicillin (1400 units per mg.) in 200,000 unit vials; (3) pure crystalline potassium penicillin (1631 units per mg.) in 100,000 unit vials.

COMPLICATIONS. A thorough study of the complications encountered is not the purpose of this study. Brief mention will be made of those conditions commonly seen. Heading the list is congestive heart failure closely followed by infarction of the kidney, spleen, lung and brain. Penicillin will eliminate the infection of bacterial endocarditis in a great majority of both early and late cases. In cases of long standing the irreparable damage done to the heart valves in the presence of myocardial damage manifests itself as uncontrollable congestive heart failure when the period of treatment is completed or shortly thereafter.¹³

Cerebral embolism is an unpredictable cause of death which occurs occasionally during the prolonged therapy. Other embolic effects are responsible for various organ infarcts. Ward⁵⁵ found a microscopic hematuria in his 18 cases, and autopsy evidence in 2 cases showed focal embolic glomerulonephritis. Further information regarding subject matter pertaining to this disease is not within the scope of this study, may be found in the selected papers appended.

CRITERIA FOR SUCCESS. As stated above, at present there are no constant laboratory or clinical findings which prove a cure.³⁶ Some claim that the leukocyte count and sedimentation rate are valuable criteria,⁴¹ while others prove these tests worthless.²¹ Success can only be measured by the increased mental and emotional stability of the patient, normal temperature and general well-being of the patient, easily determined by the attending physician.^{1,36}

It cannot be stressed too much that hope should not be abandoned for a successful outcome in apparently doomed cases. Even though the penicillin dosage rises to astronomical amounts, treatment

should be continued for as long a time as is necessary for a cure, even if this is a matter of months.^{8,14,15,30,47}

Autopsy cases of healed endocarditis show that the vegetations undergo fibrous organization.⁵² When the fibrous tissue contracts, a small elevation is left on the deformed valve. It is believed that as the vegetation becomes organized during therapy, friable fibrin masses break off and lodge in various organs.

As other antibiotics are discovered and proven clinically, their use in this disease will be of interest. Combination antibiotic therapy seems to hold even brighter hopes for the future.

Summary and Conclusions. The writer has analyzed the reports in the literature of 521 cases of subacute bacterial endocarditis treated with penicillin. Clinical arrest was effected in 371 patients (71.3%) who have continued to remain well. In an additional 95 cases (18.2%) a "cure" was produced in the hospital, but the disease recurred and the patients died within 3 to 4 months. No autopsies were performed in this group. The remaining 55 cases (10.5%) were complete clinical failures.

The following principles of treatment are amply justified by this composite experience:

1. The sensitivity of the infecting organism to penicillin should be determined *in vitro* within a range of 0.1 to 1 unit per cc.
2. If the organism is sensitive, the dosage of penicillin should be 500,000 units daily by continuous intravenous drip.
3. All cases should be treated as early as possible.
4. Therapy should be continued for at least 28 days. If the patient's condition does not improve, 1,000,000 units should be given daily for 28 more days.
5. The plasma level of penicillin and the sensitivity of the organism to penicillin *in vitro* should be determined twice a week.

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NON-ATHEROMATOUS LESIONS OF THE CORONARY ARTERIES

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NON-ATHEROMATOUS LESIONS OF THE CORONARY ARTERIES

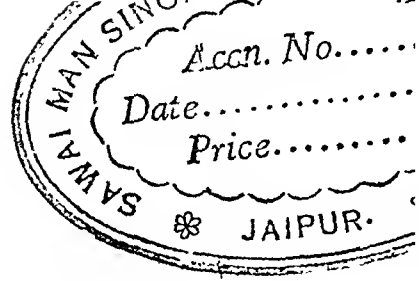
1. Congenital Anomalies
2. Medial Calcification of Infancy
3. Inflammatory Lesions
 - A. Specific Infectious Diseases
 - Syphilis
 - Tuberculosis
 - Other Bacterial Infections
 - B. Arteritis of Unknown Etiology
 - Rheumatic Fever
 - Polyarteritis Nodosa
 - Thromboangiitis Obliterans
4. Aneurysms
5. Embolic and Thrombotic Disease
6. Neoplasm

THE most important disease of the coronary arteries is atheroma. Ninety to 95% of all cases of myocardial infarction result from changes in and around an atheromatous plaque which result in reduction of the blood supply to the affected area. As a result of the recognition of this important fact, most attention, clinically and investigatively, has been devoted to the atheroma and properly so. Other lesions of the coronary arteries are clinical curiosities and scant attention has been given to them. It is the intention of this report to classify these changes and gather in one place the knowledge, especially in the way of recent advances, now scattered throughout the literature. Only the salient

features are discussed but most of the important late and key references are given for further study.

CONGENITAL ANOMALIES. Anomalies of the coronary arteries are not infrequent but are seldom the cause of symptoms. Most of the anomalies are those of origin, number, size or distribution. In almost all such cases, even when only one coronary artery is present, there is sufficient collateral circulation so that the heart functions normally. In none of Stryker's⁶⁶ cases, nor in those of Knop and Bennett,³⁰ was death directly attributable to the coronary abnormality.

Fifty-five anomalies of the coronary arteries were seen at the Mayo Clinic between 1922 and 1944.³⁰ In 3 cases, the abnormalities were multiple. There were 28 cases of accessory coronary orifices; 15 of aplasia or absence of a main coronary artery; and 15 of involvement of the coronary artery (11 of the right and 4 of the left). In 3 of these cases; the left circumflex branch was absent; in 9 there was distinct abnormality in position of origin of the coronary arteries; in 1 there was stenosis of the left coronary; in 1 the right coronary artery arose from the pul-



monary artery, and in 1, there was a single arterial trunk with a single ventricle with no aortic coronary openings but the right coronary artery arose from the carotid artery.

Stern⁶⁴ reported reduplication of the right coronary artery in a boy of 16 who died of rheumatic heart disease. There were 2 orifices side by side at the usual point of origin of the right coronary artery. The 2 vessels did not join during their course. They were both small and together their capacity was probably much less than that of a normal artery. This may have accounted for an unusually thin right ventricular wall.

It is fairly frequent for one or both coronary arteries to arise above the upper level of their respective sinuses of Valsalva. In 1000 consecutive autopsies, this condition was found in 80.⁷⁰ It is very likely that such arteries are specially susceptible to syphilitic disease of their orifices.

There are many variations in the distribution of blood to the posterior surface of the heart near the interventricular groove but these should not be described as anomalies.

Anomalous origin of the left circumflex coronary artery has been described in 4 cases.³ In each of these the right coronary artery and the left descending artery were of normal size and distribution. In 3, the left circumflex artery arose directly from the right sinus of Valsalva, immediately posterior to the origin of the right coronary artery. In the fourth case the left circumflex artery arose as a branch of the right coronary artery 1 cm. from its ostium.

Single Coronary Artery. The presence of a single coronary artery is a rare anomaly which was exhaustively studied by Krumblhaar and Ehrlich³¹ and more recently by Roberts and Loubé.⁵⁷ The latter collected 22 cases from the literature and added 9 of their own, 31 in all. Among these, the left coronary artery was missing in 17 cases; the right in 11 cases; in 3 the identity of the missing artery was not evident from the description.

For 26 patients, the age at death was

given, ranging from 3 days to 68 years. Excluding 4 children, the average age was 45 years. Thus, the absence of one coronary artery is compatible with long life. In only 6 of the series could death be related to the anomaly; in 4 there was myocardial infarction. Seventeen of the cases were in males; 9 in females; in 2 the sex was not given.

The possible mechanism for the anomaly is discussed by Roberts and Loubé. Three possibilities are given: (1) Absence of the anlage for one coronary artery; (2) a displacement of the anlage of one coronary artery so that it fuses with the anlage of the other; (3) occlusion by thrombosis, infection or maldevelopment of one coronary artery soon after its formation, with failure of subsequent canalization and with compensatory dilatation of the remaining vessels.

Origin From Pulmonary Artery. One or both coronary arteries may arise from the pulmonary artery. The literature on the subject is extensively reviewed by Kaunitz.²⁸ Two other cases were reported by Lyon.³⁶

The primitive endothelial buds which will later form the coronary arteries develop before the common arterial trunk is divided by the spiral septum into the aorta and the pulmonary artery.⁶³ A displacement of either (spiral septum or endothelial buds) may result in the enclosure of the buds within the pulmonary artery.

1. *Left coronary artery arising from the pulmonary artery.* Kaunitz was able to list and summarize in an excellent table 19 cases of the left coronary artery originating from the pulmonary artery in which the patient did not survive infancy. He added 2 more, as did Lyon *et al.*, bringing the total number of cases in this category to 23. In each case there was hypertrophy of the left ventricle, occasionally of enormous degree. Microscopically, the muscular walls show all the changes, degeneration, necrosis, fibrosis, calcification, which characterize myocardial infarction after coronary occlusion

in the adult. In addition, dilated sinuses have been found in the left ventricle (and in 1 case,⁵³ in the pericardium), which seem to communicate with the left ventricular cavity. It is possible that these represent functioning communications.²⁸

The clinical picture in most reported cases has been remarkably constant. The child seems normal at birth. Several months later there are manifestations such as dyspnea, pallor, doubling up, usually after feeding, which seem to indicate that there is pain. The picture seems definite enough to warrant the possibility of diagnosis during life, as has recently been demonstrated by Eidlow and Mackenzie.^{12a} They used 3 criteria: attacks of sweating, pallor, cyanosis, dyspnea, all seeming to indicate pain; heart enlargement; electrocardiographic evidences of infarction, inverted T₁ and ₂ and deep Q₁. Lyon *et al.*³⁶ suggested the diagnosis in their 2 cases, using similar cardiographic criteria.

Seven patients, the literature on whom is surveyed by Kaunitz, have lived to adult life, Abbott's patient surviving to the age of 64. In all cases, there were changes in the heart which followed the anomalous development of the coronary vessels.

2. *Right coronary artery arising from the pulmonary artery.* Kaunitz lists 3 such cases, in all of which the patient survived to adult life, 2 dying of unrelated causes, the third dying at 74 of congestive heart failure. In Monckeberg's case, both coronary arteries were dilated, the right being thin walled like a vein. There were anastomoses between the branches of the vessels. In Schlay's case, both vessels were likewise dilated and there was abundant collateralization of the left artery. Bennett's case was a man of 74 who died of congestive heart failure with a heart weighing 550 gm. and an old apical infarct. In this case, too, the right coronary artery looked much like a vein.

In addition to the cases mentioned here (or perhaps including the first 2 of these), Abbott¹ lists 10 patients from the litera-

ture, all of whom survived to adult life. Unfortunately, the cases are not cited.

3. *Both coronary arteries arising from the pulmonary artery.* Only 2 cases have been reported, in neither of which did the infant live beyond 10 days.^{20,34}

4. *Origin of an accessory coronary artery from the pulmonary artery.* This is of little importance since the accessory artery is but a twig supplying a limited portion of the myocardium.

Coronary artery aneurysms, presumably congenital, have been described since 1887.³⁷ They are discussed in the section on aneurysm.

In some cases, there has apparently been a persistence and growth of the intratrabecular spaces which normally are reduced to capillaries. Grant¹⁹ reported, in a girl of 14 months, blood-filled spaces in the ventricular wall communicating freely with the cavity of the ventricle and with the coronary arteries. Trevor⁶⁸ reported an intramyocardial dilatation of the right coronary artery. Soloff⁶³ reported the persistence of embryonal sinusoids and reviewed the literature.

Anomalies of the coronary veins are sometimes seen. Roberts⁵⁶ found 2 cases of "idiopathic cardiac hypertrophy" which had an anastomosis between the coronary sinus and the pulmonary artery.

Hypoplasia. There are occasional striking variations in the caliber of normal vessels. In some cases, the arterial system is uniformly hypoplastic.⁵⁵ It is probable that atheroma and its sequelae are more dangerous in such hearts.

A recent study of the embryology of the coronary arteries should be noted by all interested in congenital anomalies. Watkins⁷² has studied in detail the cardiac-coronary circulation of the 18 mm. human and found that the coronary system at that stage of development is nearly complete. The main variations are: (1) The left coronary artery is much better developed than the right. (2) The oblique vein of the left atrium, the anterior cardiac vein and the smallest cardiac veins are not as yet fully developed. (3) The

coronary sinus has not reached its definitive position.

Medial Calcification With Fibroblastic Proliferation of the Intima. This lesion, described as "medial coronary sclerosis" by Brown and Richter,⁷ apparently constitutes a distinct pathologic entity. It has been given many names, the most satisfactory of which, medial calcification with fibroblastic proliferation of the intima has been proposed by Stryker⁶⁶ who also gives a complete bibliography and adds 4 cases of his own. Field^{13a} has recently added another case.

All the cases have been in children less than 27 months old, and about evenly divided between the sexes. The media of the larger coronary vessels is extensively calcified and there is fibroblastic proliferation of the intima sometimes sufficient to occlude the artery.

Stryker concludes that the cause of this lesion is not known. "In some instances severe renal lesions are present, and in these cases the arterial lesions may represent metastatic calcification secondary to an altered calcium-phosphorus ratio in the blood. Similar lesions are sometimes found in 'renal rickets' (renal osteodystrophy). Altered calcium-phosphorus ratios likewise occur in primary parathyroid hyperplasia and in primary or destructive osseous disease, and thus these conditions also may be etiologic factors. Calcification of arteries has occasionally been observed following an intake of excessive amounts of vitamin D. Other possible causal factors that have been considered include pyogenic infection, syphilis and allergy. None of these, however, is present in all cases of medial calcification, and thus no one of them can be accepted as the sole cause. The most attractive hypothesis is that in all cases an embryonally weak protoplasm is present in these infants, and on this poor ground substance any one of many factors may act as a precipitating mechanism. Such a weakness of the protoplasm has been postulated (by H. G. Wells in E. V. Cowdry's *Arteriosclerosis—A Survey of*

the Problem) as a factor in arteriosclerosis of the adult type and may be equally a factor in the infantile type."

INFLAMMATORY LESIONS. There is little doubt that the coronary arteries, especially the myocardial branches, may be involved in the course of any infectious disease. However, little has been contributed to the literature since the descriptions of Wiesel⁷⁵ and Wiesner.⁷⁶ The latter especially suggested the possible rôle of such lesions in the pathogenesis or acceleration of atherosclerotic changes.

Arteritis may arise by extension from neighboring tissues or be mycotic in origin. Secondary thromboses may occur. Primary arteritis of the coronary vessels has been described.²⁷

Obliterating endarteritis has been mentioned by some authors.^{5,43} It is possible that such cases may have been the end result of acute inflammatory processes.

There is fairly frequent involvement of the coronary arteries in subacute bacterial endocarditis and there is a high percentage of areas of myocardial infarction in that disease.⁶²

SYPHILIS. Syphilitic narrowing of the coronary arteries is not uncommon in syphilitic aortitis and occurs in about 20% of such cases²⁶ (33%⁸). However, myocardial infarction secondary to the stenosis is rare and occurs in only 7.5%²⁶ (7.7%⁸) of cases in which narrowing occurs. In a group of 326 cases of myocardial infarction at the New Orleans Charity Hospital, only 3 were secondary to syphilis. Among cases of luetic coronary narrowing, the age range was 20 to 70, the average age was 45. Both coronaries were involved in 72.5% of cases. If only one artery is involved, it is more commonly the right. The Wassermann reaction is positive in 96% of cases. In the vast majority of cases, there is an associated aortic insufficiency. In some instances, there may be associated aortic mural thrombi and rarely, coronary embolism.⁴² Recently,⁷² a case of narrowing of the coronary orifice by syphilis, without associated atheroma

or complete occlusion but with myocardial infarction, has been described.

Syphilitic aortitis is productive and obliterative, involving all 3 coats. The process usually begins with an accumulation of small round cells around the vasa vasorum in the adventitia. The inflammation extends along smaller vessels involving the media and intima. The muscle and elastic tissue of the media is replaced by infiltration with lymphocytic and small round cells and the intima is thickened by the formation of vascular inflammatory plaques. These edematous lesions may involve the entire root of the aorta ("girdle of Venus"), involving the ostia of the coronaries where they penetrate the wall of the aorta. It is said³⁵ that the incidence of involvement of the proximal portions of the coronary arteries is high because a branch of the coronary artery supplies the first portion of the aorta where aortitis is most common. Syphilitic lesions of the coronary arteries distal to their orifices are not common.⁶⁵

Syphilitic and arteriosclerotic involvement of the same coronary artery is common. In syphilis, the lesion may be distinguished by the longitudinal wrinkling of the intima, edematous plaques around the ostia, thickening of all the coats of the vessel, patency of the terminal artery, and perivascular round cell infiltration. In arteriosclerosis, there are no Longcope plaques or intimal wrinkling and the vessels are hard and brittle containing yellow plaques throughout the length of the artery.

Syphilitic involvement of the ostia is more apt to occur if the coronary vessels take off abnormally high.³⁵ The process seldom dips down into the sinuses of Valsalva.

Weinberg and Beissinger⁷³ describe a 28 year old white woman with presumably syphilitic gummatous aortitis associated with coronary ostial stenosis and acute myocardial infarction. Kobernick^{30a} describes gumma of a coronary artery with occlusion and myocardial infarction.

Clinically, the diagnosis should be sus-

pected in every case of syphilis manifesting cardiac pain. The electrocardiogram often shows changes but these are non-specific in character unless infarction has taken place. The electrocardiogram will be affected, not by the coronary involvement as such, but by associated disease such as myocardial fibrosis or cardiac hypertrophy.

Coronary embolism in syphilitic aortitis is mentioned under the section on embolism.

TUBERCULOSIS. Tuberculosis rarely involves the coronary arteries. It is not significant as a cause of coronary occlusion. It usually occurs in miliary tuberculosis or in mediastinal or pericardial disease.¹⁸

BRUCELLOSIS. Coronary involvement is said by Manchester⁴² to occur in 26 % of his cases of brucellosis but the details are not given.

SALMONELLA SEPSIS. Barnett and Zimmerman⁵ report a case of coronary arteritis in sepsis due to infection with *Salmonella choleraesuis*, variety Kunzendorf. There was thromboarteritis of the left anterior descending coronary artery about 2 cm. from the aortic orifice with infarction of the involved myocardium. Section showed no endothelial cells. The remainder of the intima was disorganized, vascularized and infiltrated with small round cells and a few polymorphonuclear cells. The media was similarly involved and the elastic tissue was fragmented and destroyed at many points. The adventitia was heavily infiltrated and thickened. At some points, the cellular exudate consisted exclusively of polymorphonuclear leukocytes. Arteries in other organs showed evidences of inflammation.

RHEUMATIC FEVER. The literature up to 1934 was comprehensively analyzed by Karsner and Bayless.²⁷ In the following year, there appeared the excellent review by Gross, Kugel and Epstein²³ which also contains a full bibliography. Since then, there have been few systematic accounts of the effects of rheumatic fever on the

coronary arteries and few reports except for isolated case histories.

The earliest accounts were those by Bouillaud, Krehl and Romberg. Since 1900 and up to 1934, notable contributions were made by Rabe, Aschoff, Barie, Aschoff and Tawara, Geipel, Coombs, Gerhardt, Takayasu, Doubles, Thalheimer and Rothschild, Fahr, Watjen, Wiesel, Swift, MacCallum, Pappenheimer and Von Glahn, Shaw, Talalajew, Perry and Klinger, Slater. References to their papers may be found in Gross, Kugel and Epstein's bibliography.

Gross, Kugel and Epstein discuss the lesions in the myocardial arteries (those branches within the myocardium) and those in the main coronary trunks. They make a further subdivision of the lesions into those non-specific changes which seem to be an accentuation of changes normally occurring in the coronary arteries and those which are so peculiar that their presence seems to be fairly specific for rheumatic fever.

Lesions of the Myocardial Branches in Rheumatic Fever. Evolutionary changes also found in normal control cases include intimal elastification, medial elastification, fibro-elastification and adventitial fibrosis. All are conditions sometimes seen in normal hearts but occurring earlier and more severely in rheumatic fever. These lesions are found most often in the left posterior papillary muscle, less often in the interventricular septum, rarely elsewhere.

Lesions occurring either uncommonly or never in normal control cases are described as medial glossy hypertrophy, medial hypertrophy, intimal fibrosis, giant medial hypertrophy with metaplasia, medial edema, exudative and necrotizing arteritis, subendothelial hemorrhagic arteritis, net-like fibrinous thromboses of the small myocardial arteries, endarteritis verruca, granular plugged vessels, thromboses, endarteritis polyposa, Aschoff bodies and intimal musculo-elastic hyperplasia.

Lesions in the Main Coronary Arteries in Rheumatic Fever. These may occur in

any of the main arteries but are somewhat less frequent on the right side. In general, as in the case of the myocardial arteries, the normal rate of vascular retrogression is greatly increased and the changes are similar.

However, the most distinctive lesions of the main coronary arteries, found only in the active cases, are the exudative, necrotizing and other peculiar types of arteritis similar to those occurring in the myocardial arteries. Quoting from Gross, Kugel and Epstein:²³ "These lesions occurred in 10 of the 66 cases (15 percent). The exudative lesions consist of inflammatory involvement of varying grades of intensity, generally affecting the media. In some forms there may be seen marked edema of the media with swelling of the smooth muscle fibers, rounding of the nuclei with prominence of the chromatin, and the presence of inflammatory cells. In other forms of exudative arteritis the predominating cell type is the polymorphonuclear leukocyte, sometimes the lymphocyte. These cells occur either diffusely, sometimes more abundantly seen toward the intimal aspect of the vessel, or are localized in one arc of the circumference of the vessel. Ameboid streamers of polymorphonuclear leukocytes and monocytes are almost invariably seen. The latter sometimes contain fairly large nuclei with rather abundant basophilic cytoplasm. Eosinophils and mast cells are seen less frequently and irregular basophilic cells, somewhat resembling those found in Aschoff bodies, are rare.

"Together with the inflammatory cell accumulations, there was sometimes found a fibrinoid swelling of the collagen. Rupture and dissolution of the elastic membranes occurred only in the very active cases, particularly in those associated with polyarteritis nodosa. Pictures simulating rupture of the elastic membranes were occasionally found. Their significance has already been discussed under the findings of the main coronary arteries in the inactive cases.

"Both in the active and inactive cases.

inflammatory cells, generally lymphocytes, were not infrequently met with in the adventitial and periadventitial layers. In the active cases this was a more frequent occurrence, where also polymorphonuclear leukocytes, monocytes and, at times, Aschoff bodies were also present. It is of interest that these adventitial and periadventitial infiltrations occur even in the absence of macroscopic pericarditis. However, even in the inactive cases, microscopic pericarditis, *i. e.*, diffuse, rather mild lymphocytic infiltrations of the visceral pericardium, occurs with great frequency.

"While all three main coronary trunks, *viz.*, the right circumflex, left circumflex and left anterior descending, were seen involved in some of these cases, it appears that of the three the lesions were found with about the same frequency in the left circumflex and left anterior descending trunks, and least often in the right circumflex coronary artery. Apart from the above mentioned forms of exudate and necrotizing arteries (seen in six cases), proliferation of the intimal endothelial and subendothelial cells with formation of palisades was found in the left circumflex coronary artery in one case (age six years), occluding thrombosis of the left circumflex coronary artery with myocardial infarction in two cases (age 17½ months and 7½ years), verrucous endarteritis involving the left anterior descending branch in one case (age nine years), and a granular plugged lesion almost completely obliterating the left circumflex coronary artery in one case (age 25 years). Of great importance is the fact that, with the exception of the last mentioned lesion, all the inflammatory phenomena found in the main coronary vessels in active rheumatic fever occurred during the first 15 years of life. This affords additional evidence of the extraordinarily dramatic course taken by this disease in the young, a point of perhaps some immunological significance."

Inactive Rheumatic Fever. In chronic cases of rheumatic heart disease, arteritis is not found. Instead, normal retrogres-

sive changes seem to appear earlier in life and to a more advanced degree. There is a tendency toward an earlier development of heavy intimal elastic-hyperplastic and fibrotic layers, and for the appearance of heavier elastification and scarring of the media. These changes may predispose to the earlier appearance of atherosclerosis in the main coronary vessels. In any case, the vessels become more rigid and are probably less subject to vasomotor control.

It is rather difficult to evaluate the clinical importance of rheumatic coronary artery disease. According to Lowe and Wartmen,³⁵ the changes are rarely clinically significant compared to those of the myocardium. Stryker⁶⁶ did not find rheumatic involvement in his study of coronary disease in childhood, but admits that he did not study the arteries carefully in such cases. Gross, Kugel and Epstein attach much importance to such lesions, finding the damage often impressive in acute cases and they wonder whether the "vascular or primary myocardial injury is the more significant to the life of the patient." Karsner and Bayless²⁷ thought that "the relation to myocardial disease cannot be positively established but the late myocardial fibrosis is greater than is to be expected from the early acute myocarditis alone."

Nevertheless, clinically significant occlusion of a main coronary artery occurs but rarely in acute rheumatic fever. In only one of Gross, Kugel and Epstein's cases was there coronary occlusion with extensive infarction. In a 17 month old infant there was thrombosis of the left circumflex artery including the main trunk. In Rac's case,⁵⁴ a child of less than 3 who died suddenly, there were, in addition to acute rheumatic myocarditis and pericarditis, large aneurysmal dilatations in both coronary arteries and thrombosis had occurred in the aneurysm of the right coronary artery.

The relationship between childhood rheumatic fever and later occurring atherosclerotic heart disease is of the greatest

importance. The changes in Gross, Kugel and Epstein's cases of inactive rheumatic heart disease were rarely specific and there were few evidences of arteritis. Nevertheless, as previously pointed out, there was considerable acceleration of the "normal" retrogressive changes so that it is possible that such arteries might be subject to occlusive coronary disease at a much earlier age. That this may actually be the case has been suggested by several authors but there is, as yet, little statistical evidence for this hypothesis. It has been suggested, too, that coronary artery lesions, in the main trunks and in their branches, may account for some of the symptoms of angina pectoris in chronic rheumatic valvular disease.

Griffith and Huntington²² report 3 cases of abrupt death in rheumatic fever. In each case there were distinctive lesions at the base of the aorta. In 2 of the 3 there was histologic evidence of widespread vascular disease. The coronary arteries in all the cases show extreme fibrosis, cellular accumulation and "collagenous" masses in the walls of the arteries. They conclude that "the cause of abrupt death in each was an acute anaphylactic coronary angiitis superimposed upon a low-grade rheumatic carditis."

Weinstein⁷⁴ reported 10 cases of "atypical" coronary disease which he thinks may have been "rheumatic" but there were no histologic studies because his patients recovered.

Polyarteritis Nodosa. The coronary vessels are frequently (70%²³) involved in polyarteritis nodosa. Next to the renal arteries, the coronaries are the vessels most often damaged by this disease. Even Kussmaul and Maier's²² original description (1866) described such a case. In 17 of a series of 23 cases,²³ the coronary arteries were involved.

An excellent review of the history of this complication, up to 1936, and of its clinical features is that of Kerr.²³ Since that time, there have been scattered case reports, none of importance. Mintz and

Katz⁴⁴ report a case with myocardial infarction. Stryker⁶⁶ reported 2 cases.

Polyarteritis nodosa usually attacks the smaller vessels in scattered areas. The resulting infarcts are small and disseminated. Thrombosis in the affected vessel is common.

The differentiation of this lesion from that of acute rheumatic arteritis may be exceedingly difficult and the relationship, if any, between these diseases is still incompletely worked out.⁴⁶ The difficulty may be striking if, as in Stryker's case 5,⁶⁶ there are no lesions in arteries elsewhere. In such cases, the presence or absence of other evidences of rheumatic fever in the myocardium or valves may be decisive. In 4 of Gross, Kugel and Epstein's²³ cases, the diagnosis of both diseases simultaneously seemed to the authors to be justified.

The diagnosis of healed polyarteritis nodosa is beset with many pitfalls since the diagnostic criteria are so poorly defined. Nevertheless, Stryker seems convincing in his argument for placing his case 6⁶⁶ in this category.

THROMBOANGIITIS OBLITERANS. The first reported example of involvement of the coronary arteries in thromboangiitis obliterans was that of Perla.⁵⁰ Barron and Lilienthal⁶ reported another. Samuels and Feinberg⁵⁹ noted 5 cases of involvement of the coronary arteries in their series of 50 cases. Fatheree and Hines¹³ reported from the literature 40 cases in which autopsy records were available; in 10, the cause of death was coronary occlusion. Allen and Willis² found only 7 in 225 unselected cases and concluded that the incidence was no greater than in a control group. Greenfield²¹ reported a case of thromboangiitis obliterans in which recovery took place after coronary occlusion. Since the man recovered, it was impossible to state the cause of the occlusion. Mintz and Katz⁴⁴ report 1 case with myocardial infarction.

A characteristic (although not universal) feature is the presence of giant cells and infiltration with small round cells. The

lesion somewhat resembles a miliary tubercle.⁶¹

CORONARY ANEURYSM. Coronary artery aneurysm is rare except for the aneurysmal dilatations seen in polyarteritis nodosa. The literature, up to 1936, has been reviewed by Kerr,²⁹ from whom the following classification is taken in modified form. Chipps in 1942⁹ listed 45 cases in the literature and added 1 of his own. Of the 46, 36 were classifiable, he thought, as to cause: 15 arteriosclerotic, 4 luetic, 5 congenital, 1 rheumatic, 10 mycotic, 1 pure mycotic.

1. Congenital Aneurysm. (a) Dilatation at points of branching of coronary arteries. These are analogous to "berry" aneurysms of the brain.

(b) Aneurysm of the sinuses of Valsalva, with congenital defects of aortic valves. These aneurysms are often associated with bicuspid aortic leaflets or with the development of weakness of the supporting structure of the aortic valves, especially of the right ventral cusp and the forward portion of the dorsal cusp.

(c) Dilatation of branches of the coronary arteries. Seven such cases have been reported in cattle and 5 in man.²⁴ The congenital origin of some of these is doubtful. In Harris's case, the right coronary was 2 cm. in circumference for a distance of 13 cm. The absence of any other etiologic factor, such as arteriosclerosis or inflammation, and the fact that the artery communicated with the right ventricular cavity make it likely that the lesion was congenital. The patient was a male of 43 who died of brain tumor. Harris attributed the dilation to deficiency of the elastic tissue in the affected area.

2. Mycotic Aneurysm. Embolic in origin, this is seen most often in bacterial endocarditis.

3. Syphilitic Aneurysm. Aneurysms due to syphilis are exceedingly rare. Packard and Wechsler reported 3 cases.⁴⁷

4. Arteriosclerotic Aneurysm. This is the most common coronary aneurysm in people past middle age. Mitchell found

16 authentic cases in the literature and added 1 of his own.⁴⁵ The ages ranged from 32 to 77. The sex incidence was remarkable: only 1 of the 17 cases was in a female. In 13 cases the left coronary artery was involved; in 4, the right, the lesion was multiple in 3 cases but Mitchell's own case was the only one involving both the right and left coronary arteries.

In all cases, the coronary artery was the site of extensive atheromatosis and the aneurysmal sac was often filled with thrombotic material which probably helped prevent rupture. While the cause of death was cardiac in 14 cases, it was most often the result of cardiac failure or coronary occlusion. In only 5 cases was the aneurysm directly responsible for death. In 3 there was rupture into the pericardial sac causing cardiac tamponade. In 1 there was rupture into the myocardium of the right ventricle, and in 1 into the wall of the pulmonary artery.

Mitchell did not find medial muscular defects at the bifurcations such as Forbus¹⁵ had found in cerebral arteries (and, in 2 instances, in the coronary arteries). He found little reason to doubt that in his case there had been total destruction of the media by a slowly enlarging atheroma.

5. Dissecting Aneurysm. The coronary vessels may be involved either by dissection, resulting from rupture of the intima of an arteriosclerotic or aneurysmal coronary artery, or by an extension of dissecting aneurysms of the aorta. Wainwright⁷¹ reported a case of dissecting aneurysm of the aorta in which the dissection was continued into the wall of a coronary artery, resulting in coronary occlusion and myocardial infarction. In several recent cases^{38,40,41} at the Massachusetts General Hospital, an aortic dissecting aneurysm dissected back to the annulus of the aortic valves and involved the coronary orifices.

CORONARY EMBOLISM. Coronary embolism is exceedingly rare compared with thrombosis. The literature to 1932 is reviewed by Saphir.⁶⁰ Porter and Vaughan⁵² list 30 cases reported up to

1940 and add 3 of their own, in Negroes with luetic aortitis and mural aortic thrombi. Parks⁴⁸ reported an instance complicating subacute bacterial endocarditis and added several recent cases from the literature.

The embolus may consist of bacterial vegetations from the heart valves, fragments of vascular thrombi, tumor tissue, fat, air or foreign substances. It is sometimes difficult to be sure that the occluding material has not been formed *in situ* and, therefore, in order to be certain of its embolic nature, a demonstrable source and the integrity of the underlying artery should be sought. In some cases, an electrocardiogram, typical of recent coronary occlusion, may be obtained.^{12,48,62}

1. Vegetations from the heart valve, especially in subacute bacterial endocarditis, may embolize to a coronary artery. Usually the involved leaflet is an aortic. In 1 case,²⁹ the free end of a thrombotic vegetation, still attached at its base to its origin on an aortic valve, plugged a coronary artery with resulting death of the patient. A somewhat similar case, reported by Oestreich, is quoted in the same article. Mycotic aneurysms of the coronary arteries have also been reported.⁴ Microscopic emboli are apparently common¹⁰ and multiple gross emboli have been reported.¹⁷

2. Displaced fragments of thrombi may arise in peripheral veins and be carried to the coronary artery by paradoxical embolization, etc. They may arise from atheromatous ulcers of the aorta.³³ They may be formed by a fragment of a thrombus more proximal in the coronary arterial tree. In Saphir's second case⁶⁰ there was a thrombus in the proximal portion of the circumflex branch of the right coronary artery; a fragment had broken loose and had lodged in the region where the posterior descending branch comes off the right circumflex branch. Stryker's patient⁶⁶ was an infant in whom the source was not demonstrated; according to Stryker, it may have come from an umbilical vein thrombus.

3. Tumor tissue may be carried to the coronary artery as in the paradoxical embolism described by Thompson and Evans.⁶⁷

4. Fat embolism has been described.⁶⁹ While probably not as important as embolism elsewhere, it should not be overlooked as a possible cause of death after trauma. It produces "streak-like" hemorrhages in the myocardium.³⁵ Microscopically, fat droplets can be demonstrated in the small vessels.

5. Air embolism has been produced experimentally by Rukstinat and Le-count.³³

6. Foreign material accidentally injected into a vein has been known to plug a coronary artery. Zinc peroxide was found in the coronary arteries in the case cited by Von Glahn.⁷⁰

Four cases of paradoxical embolism have been reported.^{25,67,77} In 1 case there was no depletion of the pulmonary circulation or evident change in right and left heart pressure relationships, as had been considered necessary by others.⁶⁰

It is still not clear why coronary embolism is so rare. Various theories have been proposed.⁶⁰ Marie believed that the great difference between the caliber of the aorta and that of the coronary arteries might be responsible. Pavell and Benson are quoted by Saphir as believing that the right angled departure of the coronary arteries made it difficult for emboli to lodge there. According to Saphir, "the various eddies at the mouths of the coronary arteries as produced by systole and diastole, and also the peculiar flow into the coronary vessels during systole and diastole might explain the rare involvement by emboli of the mouths of the coronary arteries and of the vessels themselves." The bulk and swiftness of the blood current in the aorta and the fact that most coronary filling is in diastole may be factors.

Chippis² says that since DeNavasquez has "shown that minute emboli frequently enter the coronary arteries, it is clear that the size of emboli large enough to occlude

the main coronary branches must be the factor determining the rarity of gross coronary embolism. Emboli of sufficient size are probably not nearly as numerous in bacterial endocarditis as are minute emboli. If a great many emboli of microscopic proportions are released into the blood stream and thoroughly mixed, then it is obvious that the number of these emboli entering the coronary arteries will be in proportion to the coronary blood flow. On the other hand, larger emboli of exactly the correct size to occlude one of the coronary arteries or its main branches will much less frequently be released from the endocardial vegetations.

"When an embolus of exactly the right size is released, it will, by reason of its size, have greater difficulty in entering the coronary arteries, for its dimensions must be nearly as great as the diameter of the coronary orifices. The difficulty of its entrance into the coronary orifices may be illustrated by analogy with a device used by small boys in gambling with marbles. This device consists of a cigar box with a round hole cut in its lid, large enough to admit a marble freely, providing that the marble is dropped straight through the hole. However, unless the aim is accurate, the marble strikes the edge of the hole, bounces away and does not enter the box. In the same way, an embolus only a little smaller than the coronary orifices does not enter unless it is carried directly into the orifice

without being deflected by impact with its margins."

Thrombosis. There seems to be little doubt that, as originally proposed by Rokitansky, thrombosis will effect changes in the wall of the surrounding vessel. Interest in these changes has recently been revived by the work of Duguid,¹¹ who even ascribes to thrombosis a rôle in the pathogenesis of coronary atherosclerosis. This will probably be a fruitful field for future investigation. It seems to me entirely possible that certain systemic diseases, such as sickle cell anemia and polycythemia vera, which cause thrombosis and sludging in small arteries, may cause changes in the walls of the arteries after a period of time. It should be noted at this point that Merkel^{43a} has reported plugging of a coronary artery by *Plasmodium falciparum* with ensuing myocardial infarction.

Neoplasm. Neoplasm involving the heart may press on the coronary artery or may invade it, in either case causing occlusion. Appelbaum and Nicolson⁴ reported a case in which the right coronary artery was completely occluded. In Fishberg's case¹⁴ the left circumflex artery was partially occluded by pressure from surrounding tumor tissue. The patient had had cardiac pain. Peppard and Larson⁴⁹ reported a case in which both coronary arteries were narrowed by surrounding sheaths of neoplasm, metastatic from cancer of the breast.

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NEUROLOGY AND PSYCHIATRY

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THE IATROGENIC FACTORS IN ILLNESS

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THE term "Iatrogenic" (Gr. *iatros*, doctor, and *gen*, producing) disease has been aptly described by Dorland's dictionary⁴ as a "disorder induced in the patient by the physician, based on the physician's examination, manner or discussion." Relatively few articles on this subject have appeared in the literature. In his instruction to students and staff doctors, Dr. Franklin G. Ebaugh⁵ has always emphasized the rôle of the iatrogenic factor in the causation, continuation and calcification of psychoneurotic states and symptoms. During World War I, the accepted use of the serious sounding term "shell shock" for all types of psychiatric conditions appearing in or near the combat area resulted in many patients clinging to their symptoms for years or permanently. In World War II the term "exhaustion" was used at the army level for this same class of combat psychiatric casualties. Hence, when these patients read their diagnoses on their emergency medical tags (which were tied through a button hole of the shirt or combat jacket) the relatively benign term "exhaustion" suggested a condition of transient character. The groundwork was thereby laid for the prompt return to duty of all but the more severe anxiety reactions and the few psychotics. Those patients who were evacuated to the rear from division clearing stations to the army psychiatric treatment center found themselves in an environment where no organically sick or

wounded patients were treated. Thus, there were fewer unconscious "additions" of symptoms from other patients than there would have been otherwise. The complete absence of nurses in these treatment centers further diminished the feeling among the patients that they were seriously sick. In at least one of these psychiatric treatment centers, at the army level, a "team" consisting of an internist, a gastro-enterologist and a psychiatrist was established to diagnose and treat certain patients with obscure symptoms referable to the gastro-intestinal tract. Concurrently with the usual organic investigation a detailed study of the psychologic structure and life situations of the patients was made. Definitive diagnostic and treatment procedures were thereby rapidly established at that one location and many patients were saved from the endless series of Roentgen ray examinations and laboratory studies that might have followed their evacuation through the usual medical channels. Repeated examinations for organic disease suggest to the patient that he must have some rare organic condition which is puzzling even to medical men. This is a prime cause of chronic invalidism.

It is realized that the problems met with in military psychiatry and the methods available to combat them are not entirely identical with those seen in the practice of civilian psychiatry. However,

many of the fundamental principles are the same.

Anxiety has been called the nucleus or core of all psychoneuroses. When the psychologic and physiologic aspects of anxiety are experienced by the patient, and only the physiologic aspects are observed by the physician, such a psychoneurosis is termed an anxiety state. It manifests itself by such subjective symptoms as awareness of danger or fear, often apparently unmotivated and occurring during the day or night, and is experienced as diffuse discomfort which is characteristically accompanied by tachycardia, tremors, globus, dyspnea, faintness, vertigo, perspiration, nausea or vomiting, and urgency of urination or defecation.³ Many factors may serve as precipitating or trigger stimuli to make this type of psychoneurosis apparent to both patient and physician. These factors may be overwhelming and catastrophic experiences or they may be relatively trivial in susceptible individuals. They may be purely physical, such as poor nutrition, fatigue, exhaustion, or accident, or they may be largely emotional factors, such as sexual difficulties or frustrations, guilt feelings, frustrated ambitions, discouragement or fright. At any rate, anxiety states are frequently erroneously diagnosed and treated by the general medical profession for thyrotoxicoses, "heart attacks," gall bladder disturbances, hyperinsulinism, etc.⁴ The symptoms are precipitated, exaggerated and prolonged by doctors' comments and actions which suggest organic disease. These cases are always made worse and sometimes incurable by surgical procedures.

A large percentage of psychoneuroses fall into the category of "somatization reactions."⁵ In this type of neurotic response the anxiety, inherent in all psychoneuroses, is translated into functional disorders of specific organs of the body, thereby freeing the patient to a large degree from the disagreeable subjective sensations of anxiety. The visceral responses include disturbances in the gastro-

intestinal tract, cardiovascular apparatus, skin, genito-urinary tract, sexual functioning, endocrine system, as well as allergies of various kinds. Bowel conscious patients often demand rigid diets, drugs and operations of all sorts.² All of these medical and surgical procedures tend to fixate hypochondriacal ideas. The great multitude of victims of polysurgery in this country is disgraceful testimony to the inadequacy of our average medical curriculum, which overemphasizes organic pathologic changes and ignores emotional factors as causative of gastro-intestinal symptoms. Where symptoms referable to the heart are concerned, the situation is even worse. Many patients have been told by their physicians, for example, that they had a "murmur," a "leaking valve," or "a leaking heart" with no investigation beyond auscultation of the heart. Doubt as to the integrity of the heart is a very frequent cause of chronic incapacity and a type of disability that is extremely difficult to alleviate.¹ Genito-urinary complaints in both male and female neurotics are often treated surgically, medically or in combination. The prostate gland is too often treated for impotence, venereal phobias and other psychosexual problems. Hysterectomies are too often performed for such psychogenic conditions as fear of pregnancy, frigidity and guilt over various psychosexual conflicts. Psychotherapy is made much more difficult after the production of an artificial menopause or sterility.²

The following are some of the cases seen in this clinic that demonstrate how physicians themselves have unwittingly initiated or contributed greatly to incapacitating illness:

Report of Cases. CASE I. M. D. G., a 32 year old white woman was hospitalized at the Colorado Psychopathic Hospital from July 14 to November 6, 1943 because of paranoid schizophrenia. She was given a complete course of insulin coma treatments and was discharged remarkably improved. Upon her discharge from the hospital her husband immediately obtained a divorce and left her

with two small children to support. As she had difficulty in maintaining an adequate economic status, she placed her two small children in a Denver orphan's home and went to California in June, 1944. While in California she experienced her first acute anxiety attack which she described as being "just like when I had been severely frightened, although when I had the spells there was nothing to be frightened about." These attacks occurred on the average of 2 or 3 times per week and lasted as long as several hours. She obtained maximum relief by bed rest. Her anxiety attacks were manifested by palpitation, tremor and near syncope. She consulted a local physician about these attacks and was told, "You may have had such a severe heart attack that you barely escaped death." He started her on digitalis and kept her "digitalized" for several months until she ran out of funds to pay the bill. Since the anxiety attacks continued, she consulted another physician who stated, "You have angina pectoris." This second physician advised immediate hospitalization. At this point the patient became somewhat dubious and consulted the Stanford Medical Clinic in San Francisco. She was told that her difficulty was functional and was advised to continue with psychiatric guidance in Colorado. She has been followed on an outpatient status since December, 1946. Although at times she gives lip service to the fact that her cardiac symptoms might be on a functional basis, she still entertains the possibility of having organic heart disease because she had been told so by two previous physicians.

Her anxiety appears to be associated with unrecognized guilt feelings centering around the economic necessity for rejecting her two small children by placing them in an orphan's home. Since her return to Colorado, with frequent visits to the orphanage, her anxiety attacks have diminished in severity, frequency, intensity and duration.

CASE 2. M.D., a 38 year old white divorcee entered Colorado General Hospital with the diagnosis of "toxic thyroid." On admission she complained of hot flashes since the age of 15, exhaustion for 6-7 years, "nervousness" with tremor for 4 years, insomnia, and palpitation on exercise. An enlarged thyroid was readily palpable. There was a slight tremor of the upper extremities with no hyperhidrosis. Her B.M.R. was plus

5. Blood chemistry was normal. Her pulse was continuously between 70 and 80 per minute. There was no temperature elevation. Her blood pressure was 130/90. She entered the hospital for surgery on the advice of a local physician who had told her, "You have a toxic thyroid and an operation will solve all your problems."

It was thought by the surgical and psychiatric staff that this patient had a benign adenoma of the thyroid which was not toxic. Psychiatric study revealed that she was married at the age of 32 to a man 11 years her senior who had been married 4 times previously. She stated that "he was an alcoholic, a psychopath and a genius and too much for me." She said that her marriage had been a failure from the start, and that her husband was "sadistic and dependent." She recognized that she had many emotional problems and declared, "My nervousness is what is wrong with me. If an operation is what I need to get me over it, that is what I want. If an operation won't do it, I want whatever will make me well." It was explained to her thoroughly by the surgical and psychiatric staff that they would be glad to have her thyroid tumor removed, but that it certainly would not solve her emotional problems and anxiety symptoms. She accordingly underwent surgery for the removal of the benign adenoma. Pathologic examination of the thyroid tissue removed failed to reveal any toxic changes. She obtained some slight relief in the sense that removal of the tumor ended 15 years of mild concern about it. However, her emotional problems and resulting anxiety symptoms remained practically unchanged. Upon her release from the hospital she stated that she intended to try Christian Science for several months, and, if this failed to bring her the desired relief, that she would return to the hospital to consult a psychiatrist.

CASE 3. A 23 year old white single girl entered Colorado General Hospital on March 7, 1945, complaining of severe fatigability and a daily low grade fever of two years duration. She had been bedridden most of that time. The patient first noticed excessive fatigue and "nervousness" during her high school years. These feelings continued during two years at Denver University and into the years 1941, 1942, and the spring of 1943. She first consulted a physician in the spring of 1942 for "nervousness, tiredness

and a pounding in my head." Her doctor told her that she had high blood pressure and a heart murmur, and said that her diagnosis was rheumatic fever. During the next year she consulted several other doctors who diagnosed her as having rheumatic heart disease, tuberculosis, and brucellosis. Finally she felt so sick and tired that she went to bed and remained there as a chronic invalid for 2 years. During the last few months prior to hospitalization she had been taking Digifortis.

Her family history revealed that her mother had been a chronic invalid for years and had been bedridden with tuberculosis for 7 years during the patient's childhood. The patient's only sister, 2 years older, was also seen in the clinic and proved to be a very maladjusted individual. Physical examination of the patient showed a blood pressure of 140/95, temperature of 100.2° F., pulse of 108, and respiration 24. She exhibited marked vasomotor instability, dilated pupils, and sweaty palms. There was a functional systolic murmur. Blood and urine were normal. Electrocardiogram, chest film, blood cultures and agglutination tests were entirely negative for organic disease. The Psychiatric Liaison Department was asked to see her because of the possibility of her having a psychoneurosis.

After a psychiatric interview of about 20 minutes she left the hospital with marked subjective improvement and remained out of bed during that week end. She then returned to the hospital alone and ambulatory, and was interviewed on two occasions that week. At the end of the week she was almost completely free of her disabling symptoms. Her temperature, taken 4 times daily for a week, was normal for 4 days, with scattered elevations up to 99.4° F. for 3 days. A follow-up on this patient revealed that she has been clinically well since shortly after leaving the hospital and has not been bedridden since then.

This case illustrates the value of prompt psychiatric consultation where symptoms of the sort seen here present themselves. This healthy, fairly well-balanced girl wasted two years of her life in bed and spent a large part of the family income consulting a host of physicians who gave attention only to the organic tradition in medicine.

The history was simply that of a sheltered, protected and pampered girl who was

reared in a rigid religious environment. She had an invalid mother and an odd, frustrated and complaining older sister. When she began to step out and enjoy herself, her sister became more complaining, unpleasant and reprimative. Finally, she developed exaggerated feelings of guilt over minor intimacies with a soldier, the first real "steady boy friend" she had ever had. The soldier suddenly stopped seeing her, moved out of town and dropped completely out of her life. It was at this very time that her symptoms became severe enough to force her to give up her work and go to bed. Until her conversation with the psychiatrist she suspected no connection between her frustrated love affair and the development of bodily symptoms and signs.

CASE 4. T. M., a 19 year old white single male, was admitted to Colorado Psychopathic Hospital on September 6, 1946, because of feelings of tension, "nervousness," tremulousness and suicidal preoccupations. On admission he was resistive and hostile. It was revealed that prior to his hospitalization he had indulged in the compulsive purchasing of several hundred pairs of men's hosiery. He was an immature over-dependent individual with rigid perfectionistic traits. He was evaluated by the entire staff as having an acute schizophrenic reaction with latent homosexuality in which his homosexual drives were channelized by the repetitive purchasing of men's hosiery. He improved markedly under individual psychotherapy and was discharged from the hospital 22 days after admission. Around Christmas of 1946 he married a woman 18 years his senior in order to attain sufficient economic security to pursue a course of instruction which would qualify him as a beautician. Several weeks later he became tremulous, tense and anxious, and also complained of a "tight feeling in my stomach." Upon pressure from his family he was sent to his family physician who promptly informed him that he was suffering from "thyroid disease." He was placed on a routine of Lugol's solution and vitamin injections prior to the regular follow-up visit with his psychiatrist.

Treatment for "thyroid toxicosis" has only served to fixate his attention on hisoma. The trusted family physician had unknowingly converted a case of anxiety reaction with a reasonable prognosis under

psychotherapy into a more rigid psychoneurotic pattern which is extremely difficult to treat. This is a case of acute anxiety partially channelized in terms of the compulsive purchasing of men's hosiery. He suffered an acute psychotic episode from which he quickly recovered with adequate psychiatric care and guidance. At the present time his marriage to an older woman presents a threat to his adequate adjustment, and he has developed somatic repercussions of anxiety.

Summary. 1. A brief account of some of the methods used by military psychiatrists during World War II to prevent the continuation and calcification of psychoneurotic symptoms is presented.

2. The symptomatology of anxiety and its relation to functional disorders of specific organs of the body is discussed.

3. Four cases are discussed to show how doctors who are concerned only with the organic side of medicine can actually prolong a patient's illness indefinitely. In addition, mistakes in the diagnosis of psychoneurotic disorders encourage patients to make the rounds of doctors and eventually of cultists and quacks. The primary cause of these mistakes lies in the failure of medical schools to give the emotional side of illness its proper emphasis.

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PHYSIOLOGY

PROCEEDINGS OF

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Dynamic Structure of Glucose Convulsions. M. WIERZUCHOWSKI, T. TOCZYSKI, and J. SYSA (Physiological Institute, Medical Faculty, University of Lodz, Poland). Hyperkinetic phenomena evoked by high concentrations of glucose in the blood and tissues appear during chloralose anesthesia almost in the same form as in the normal unanesthetized dog (M. Wierzuchowski, *J. Physiol.*, 87, 85, 1936; R. A. Cutting, P. S. Larson and A. M. Lands, *Arch. Surg.*, 38, 599, 1939), but at somewhat lower blood glucose levels (2100 mg. %). At the acme of convulsions movements occur in all the striated muscles of the body and also in some smooth muscles. Because they are depressed by lack of O_2 and excess of CO_2 , they seem to be of central origin. This is proved by experiments with one hind leg isolated vascularly but with intact nervous connections. When the trunk of such a dog is injected with glucose and the isolated leg fed by another dog having normal blood sugar level, the perfused leg shows convulsions of the same shape as appear in the other hyperglycemic leg of the same dog. There exists an increase of reflexes in the beginning of hyperkinesia but the reflexes may even disappear completely towards the end of convulsions. They seem, however, not to be connected with irritation of the afferent or interneuron connections.

The fits persist after removal of the brain cortex. In decerebrated animals and in dogs with the cervical spinal cord cut they appear as well below as above the level of section. In the last case when the spinal cord is severed during convulsions, sometimes almost no shock phenomena appear and the twitches continue as well below as above the section plane. That in this case there is no shifting of the site

of convulsions from the higher levels of the neuraxis to the lower ones at the moment the section is made, is proven after vascular isolation of the head down to the cervical level with intact connection of the spinal cord with the brain. When such a head is perfused by another animal in which glucose concentration is being raised to the convulsive level, convulsions appear in the isolated head obtaining high glucose supply, but not in the rest of the body having normal connections with the hyperglycemic brain through the intact spinal cord. Convulsions therefore originate only in the levels of neuraxis which are in contact with high glucose and the sites of their origin seem to be distributed equally along the whole neuraxis at various segmental levels, each of them having its own sensitivity towards the convulsive stimulus.

After reaching the acme, convulsions slowly decrease when the glucose concentration in the blood is being further raised. They finally cease at some 4000 mg. %, but the motor neurons still obey impulses coming from the higher centers, for spontaneous respiration further persists (M. Wierzuchowski, J. Sysa and T. Toczyski, *Abstracts of Comm. XVII International Physiological Congress*, Oxford, p. 257, 1947).

As to the nature of active stimulus information is obtained from the continuous drop of the intracranial pressure when blood glucose level is raised continuously, indicating shrinkage of the brain substance and probably its dehydration. As similar convulsions were obtained during intravenous injection of high amounts of sodium chloride, the active stimulus in both cases is the increased osmotic pressure. Under highest glucose saturations in the

body, almost a doubling of the osmotic pressure of the blood serum was found. For such conditions we suggest the name of hypermoleculosis.

The Rate of Increase of Arterial Oxygen Saturation During Inhalation of Oxygen.

W. S. FOWLER, M.D., and J. H. COMROE, JR., M.D. (Dept. of Physiology and Pharmacology, Graduate School of Medicine, Univ. of Penna.). Continuous measurements of arterial oxygen saturation (Millikan oximeter) and nitrogen content of the respired gases (Lilly-Hervey nitrogen meter) were made in 42 normal adults following the change from breathing room air to breathing 99.6% oxygen. Alveolar pO_2 exceeded 160 mm. Hg within 1 to 3 seconds, lung to ear circulation required about 7 seconds and oximeter lag was 6 seconds. Maximum arterial saturations were not recorded until 52 seconds (average), indicating a 35 second delay between expected and actual achievement of maximum saturation. Voluntary hyperventilation with O_2 decreased the delay. To test the possibility that the delay was due to uneven gas mixing in the lung, 14 subjects breathed 40% O_2 for 5 to 7 minutes, with and without hyperventilation, then breathed 99.6% O_2 . In all cases, a significant further increase (mean 0.85%) of saturation followed pure O_2 inhalation. These results suggest that neither (1) venous-arterial shunts, (2) uneven lung mixing, nor (3) Hb reduction from ear metabolism are adequate explanations for the delay, but may indicate that alveolar and arterial oxygen tensions greater than the customarily accepted level of 160 mm. Hg are required to completely saturate Hb. The shape of the oximeter curves, (1) on breathing oxygen, and (2) when breathing of room air is resumed suggest a reciprocal relationship between reduced Hb and pO_2 .

The rise of arterial saturation is the end-result of several processes: movement of O_2 to alveoli, involving lung gas mixing; diffusion of O_2 across the alveolar membrane into the red blood cell; conversion

of reduced Hb to HbO_2 ; transport of HbO_2 to the site of measurement. Disturbance of these functions in cardiorespiratory disease was reflected in a delayed rate of arterial saturation increase on breathing oxygen.

The Effects of Frontal Lobotomy on the Cerebral Blood Flow and Metabolism.

HENRY A. SHENKIN, M.D., RACHEL B. WOODFORD, M.D., F. A. FREYHAN, M.D., and SEYMOUR S. KETY, M.D. (Depts. of Surgery, Psychiatry, and Pharmacology, Univ. of Penna.; and the Delaware State Hosp., Wilmington, Del.). The nitrous oxide technique for the measurement of the cerebral blood flow was applied to 7 psychotic patients before and after frontal lobotomy. The study was done within the week preceding operation and from 13 to 33 days after operation. The cerebral blood flow was found to be significantly decreased following operation from an average of 56 to 43 cc./100 gm. brain/min. (23%). The cerebral oxygen consumption was also significantly lowered by 16% from 3.6 to 3.1 cc./100 gm. brain/min. The cerebrovascular resistance was found to be markedly increased following frontal lobotomy. The increase averaged 23% from 1.7 to 2.1 resistance units. No significant change was found in the mean arterial blood pressure, nor in the carbon dioxide, or oxygen contents of the arterial or internal jugular blood following frontal lobotomy. It seemed clear that the cerebral blood flow resulted from the increase in the cerebrovascular resistance. The increase in cerebrovascular resistance could possibly be related to the decrease in cerebral metabolism, but the data did not clearly indicate this relationship. The decrease in cerebral metabolism seemed to be more likely the result rather than the cause of the lowered cerebral blood flow. This was supported by a slight increase in arteriovenous oxygen difference indicating a relatively lowered oxygen supply to the brain following lobotomy. An equally feasible theory for

the reduction of the cerebral metabolism following lobotomy is that operation interrupted important association pathways leading to a decrease in the total number of stimuli playing upon the cerebral neurons with the lowered activity reflected in the lowered cerebral metabolic rate.

The Standardization of Hemoglobin Measurement. DAVID L. DRABKIN (Dept. of Physiological Chemistry, Graduate School of Medicine, Univ. of Penna.). In a continuation of our work upon the standardization of hemoglobin,¹ it has proved desirable to secure an independent (non-hemoglobin or hemin derivative) method for the standardization of hemoglobin measurement, as well as of the instruments used for this purpose. The increased popularity of photoelectric photometry, and the probable replacement of older "colorimetric" procedures by the more modern photometric techniques has made it advisable to seek a standard applicable to the use of the photoelectric filter photometers.

Drabkin and Austin's spectrophotometric standard² of eupric ammonium sulfate (CuSO_4 in 2N NH_4OH) has, accordingly, been successfully adapted for the standardization of hemoglobin measurement. The standard may be prepared from either high-grade, non-deliquescent crystals of $\text{CuSO}_4 \cdot 5 \text{H}_2\text{O}$, or, more elately from Bureau of Standards copper.³ Conversion factors have been obtained from the ratios of the optical densities, D values ($= -\log$ transmission), of 0.012 M $\text{CuSO}_4 \cdot 4\text{NH}_3 \cdot \text{H}_2\text{O}$ and of 0.035S mM/L oxyhemoglobin, HbO_2 , also of 0.035S mM/L cyanmethemoglobin, MHbCN , for 3 types of spectrophotometers, the Bausch and Lomb polarization (3 instruments checked) and the Beckman photoelectric (2 instruments checked); the Hardy automatic recording instrument, and 2 filter photometers, the Evelyn (2 instruments checked) and the Klett-Summerson (6 instruments checked). With the spectrophotometers, the wave-length setting was at 540 m μ .

With the filter photometers the green filters, with maximum transmission at λ 540 m μ were used. The concentrations chosen for the copper salt standard and the cyanmethemoglobin (a measure of total pigment³) were such that with the Bausch and Lomb spectrophotometer identical D values were obtained for the 2 solutions. The concentration of 0.035S mM/L of HbO_2 or MHbCN is that yielded by a sample of blood, originally containing precisely 15 gm. of hemoglobin per 100 ml., diluted 1 to 251 (as with a standardized capillary pipette of 20 c.mm. capacity, washed out into 5 ml. of solvent).

Owing to the fact that the usual filters in filter photometers have a broad spectral span, the ratios of $D_{\text{HbO}_2}/D_{\text{Cu}}$ standard of $D_{\text{MHbCN}}/D_{\text{Cu}}$ standard ($= 0.984$ and 1.080 respectively for the Klett-Summerson instrument) once established can be used for that particular type of instrument. For each type of filter photometer they are independent of the character of individual photocells, test-tube cuvettes, and filter. This has been verified on several instruments of each type, as has been stated. In our hands the determinations with the separate instruments agreed within $\pm 1\%$.

Thus, an Evelyn or Klett-Summerson filter photometer is calibrated for hemoglobin measurement by means of the gravimetrically prepared independent standard of $\text{CuSO}_4 \cdot 4\text{NH}_3 \cdot \text{H}_2\text{O}$. The D value for blood containing 15 gm. of hemoglobin per 100 ml. is then obtained by the use of the conversion factors, which we have determined. The advantages of this method of standardization of hemoglobin measurement need not be enumerated. However, it may be pointed out that the method has far broader photometric analytical possibilities.

In 67 male and 15 female freshmen of the School of Medicine, University of Pennsylvania, the hemoglobin content of the capillary (finger-tip) blood, sampled by means of calibrated 20 c.mm. pipettes from May 23 to 30, 1946 (mean room temperature $= 25.5^\circ \text{C}$.), 3 to 4 hours after

breakfast, with the subject in the sitting position, was found to be respectively 16.3 (S.D. = ± 0.9) and 14.5 (S.D. = ± 1.1) gm. per 100 ml.

In an earlier series (December, 1944)

blood samples obtained after dinner from 38 male students by venipuncture and diluted macro-volumetrically had a hemoglobin content of 15.5 (S.D. = ± 0.8) gm. per 100 ml.

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NOTICE

TO THE SUBSCRIBER TO THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DUE to the increased costs of material and labor, we find it necessary to increase the subscription price of *The American Journal of the Medical Sciences* to \$8.00 per annum beginning January 1, 1948.

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BOOK REVIEWS AND NOTICES

FOOD REGULATION AND COMPLIANCE. By ARTHUR D. HERRICK, Member of the New York and Federal Bars. Vol. II. Pp. 655. New York: Revere Publishing Co., 1947. Price, \$10.00.

VOLUME I of this set appeared in 1944 and concerned itself primarily with the various aspects of food labeling, packaging, grading and advertising under the Federal and State laws governing the same. Such laws seek also to prevent the distribution of adulterated, deleterious and unwholesome foods. The present volume discusses food regulations concerned with the actual production, processing, packaging and storage of foods.

Most of the discussions are limited to the Federal Food, Drug and Cosmetic Act and the various directives and court interpretations of this body of law. Approximately half of the volume is devoted to mode of administration, controls, enforcement means, offenses and violations, criminal prosecution, seizure and injunctive proceedings. An appendix abbreviates the Federal Act and the general regulations for its enforcement.

The book will be of value primarily to producers, processors, and distributors of foods to the public. H.V.

WHAT IS PSYCHOLOGY: A BASIC SURVEY. By WERNER WOLFF, Professor of Psychology, Bard College, Annandale-on-Hudson, N. Y. Pp. 410; 39 figs. New York: Grune & Stratton, 1947. Price, \$4.00.

THE writer states that psychology "deals with man's inner experiences and his behavior, with the interrelationship of both, with the organs influencing experience and behavior, and with the relationship of the experiencing and behaving individual to his environment." Much space is accorded the psychoanalysis of Freud, together with the teachings of two of his leading followers—Alfred Adler with his individual psychology, and Carl Jung with his analytical psychology. In the chapter on Thinking, in a discussion of the conditioned reflex phenomenon, it is stated: "All involuntary reactions such as breathing, heartbeat, reactions

to heat and cold, might be regulated, and that this is actually possible is shown by a method which has been used for thousands of years by the Hindus, the method of Yoga." By the way, Freud's "depth psychology" would not be considered sufficiently deep for Yoga.

"There is much disagreement as to a detailed definition of the term 'personality.' G. W. Allport is quoted as listing more than fifty definitions." This statement is followed by much criticism of various definitions; but the writer has none of his own to offer. The same is true in the discussion of "intelligence." However, early in the book we are warned that psychology is a science of contradictions. There is a bibliography of 21 pages and an ample index.

N. Y.

BUCHANAN'S MANUAL OF ANATOMY. By F. WOOD JONES, D.S.C., *et al.* 7th ed. Pp. 1616; 38 ills. Baltimore: Williams & Wilkins, 1946. Price, \$10.00.

THIS book is precisely what it professes to be, a manual of topographic anatomy. The subject is well covered, yet it is presented in a clear and concise manner with a minimum of unnecessary detail. The bones are discussed at the greatest length in a series of chapters at the beginning of the book. The remainder of the volume is devoted to a topographic survey of each region of the body in turn, each structure in a given region being described and its relationships presented.

Very little histology or systematic embryology is included. The latter is disposed of in a single concise chapter. Histologic features are but briefly mentioned in conjunction with the gross descriptions.

The illustrations are black and white line drawings. While simple, and occasionally somewhat crude, they are clear and to the point, and they serve their purpose well. A few roentgenograms are also included.

An appended glossary and series of bibliographical notes are especially valuable.

A. B.

THE PROCEEDINGS OF THE CHARAKA CLUB.
Vol. XI. Pp. 243. New York: Richard R.
Smith for The Charaka Club, 1947. Price,
\$7.00.

THE 24 contributions put forth in this volume date from 1940 to 1944, and about an equal number read before the Club are listed by title only. Continuing the aims for which this unusual organization was founded almost half a century ago by Collins, Dana, Holden and Sachs, its programs exhibit varied expressions of culture indeed. Medical history, essays, biographical sketches—including memoirs of 6 deceased members—poetry, fiction, accounts of travel are some of the fields represented. Mention of individual items for the present volume would serve no useful purpose—an exception must be made, however, in favor of the sprightly essay on "The Lamentable Decline in Self Satisfaction," presented in 1940 but even more applicable today than in that distant time. Suffice to say that, contrary to what one so often finds in scientific articles, these are uniformly well written, and few are without some general interest. Let us hope that a semi-centennial volume is already in the making, and that this distinguished group will continue its activities into the far future for the delectation of the general public as well as of its own members.

E. K.

THE PERIPHERAL CIRCULATION IN HEALTH AND DISEASE. By ROBERT L. RICHARDS, M.D., Rockefeller Fellow in Medicine; formerly Assistant Physician, Neurovascular Unit, Gogarburn Hosp., Edinburgh. Pp. 153; 104 figs. Baltimore: Williams & Wilkins, 1946. Price, \$6.00.

THIS book contains much information on the physiology and functional pathology of the arteries and the vasomotor nerves. The greater part of the book is devoted to a study of the response of the skin temperature of the extremities to cold and reflex heat and to diagnostic nerve block. The vasomotor responses of patients with organic arterial occlusive disease and with Raynaud's phenomenon are discussed in detail. A chapter is devoted to the vasomotor response in patients with peripheral nerve injuries. Much information is present here which should be valuable in studying these patients, particularly in determining the degree of

nerve injury and the rate and amount of nerve regeneration as manifested through studying the vasomotor response in the digits and extremities. The final chapter are concerned with the immersion foot syndrome. This book should prove of considerable value to those who are especially interested in diseases of the peripheral blood-vessels and nerves. One comment that might be made is although the volume claims to discuss the peripheral circulation, it devotes no space to diseases of the veins. This is a common error in the titles of papers and books. M. N.

BONE AND BONES. FUNDAMENTALS OF BONE BIOLOGY. By JOSEPH P. WEINMAN, M.D., and HARRY SICHER, M.D. Pp. 464; 289 ills. St. Louis: C. V. Mosby, 1947. Price, \$10.00.

THIS is an interesting book in a field heretofore largely neglected; that is, the biology of bone. The authors devote 2 chapters to normal structure of bone and the major portion of the book to its pathologic conditions. Most of the affections of the skeletal system are discussed from the endocrine, vitamin and mineral effects and infection, traumata and tumors of bone. It should be a very valuable guide to those interested in bone and joint pathology, though it is to be hoped that the cuts will be more clearly reproduced in subsequent editions. In spite of this the book is a useful treatise on a much neglected topic and the combined efforts of the anatomist and pathologist have produced a very worthwhile volume. P. C.

RETINAL STRUCTURE AND COLOUR VISION. By E. N. WILLMER. Pp. 231; 77 figs. London: Cambridge Univ. Press; New York: Macmillan, 1946. Price, \$4.50.

THE author reviews the current histologic and cytologic picture of the human retina. He points out the differences in the structure of the rods and cones and their neural connections, based on the current conceptions of Polyak, and their functions are discussed. On the basis of sensitivity curves, there seems to be little doubt that the retina contains 2 separate sets of sensory elements, each responding in different degrees to all

wave lengths of the visible spectrum which fulfills the minimum requirements for the discrimination of intensity in wave length. Keeping this in mind, in the rest of the book the author attempts to bring into line the known data of color vision in terms of stimulation of these 2 retinal receptors. This theory necessitates postulating the existence of 2 separate types of rods, (1) those, connected with visual purple, which function in dark adaptation, and (2) a non-adapting or "day rod" which have either never acquired or have lost the power of dark adaptation, although they still depend for their spectral sensitivity upon visual purple. These 2 types of rods, plus the cones, each would have its own spectral sensitivity and thereby fulfill the essential condition for complete color vision.

The book is well written and the author presents a convincing hypothesis. He, himself, admits and points out the weaknesses in his hypothesis. It should be read by all who are interested in the subject of color vision.

F. A.

ADVANCES IN PROTEIN CHEMISTRY. Vol. III. Edited by M. L. ANSON, Continental Foods, Hoboken, and JOHN T. EDSALL, Harvard Medical School, Boston. Pp. 524. New York: Academic Press, 1947. Price, \$7.50.

To keep acquainted with the changing and growing fields of protein chemistry articles of the type contained in this volume is a necessity. Each author has presented a comprehensive treatment and critical evaluation of the subject within his special field of endeavor. The following topics are reviewed: (1) Transamination and the Integrative Functions of the Dicarboxylic Acids in Nitrogen Metabolism, by Alexander E. Braunstein. (2) Ferritin and Apoferritin, by Leonor Michaelis. (3) Adsorption Analysis of Amino Acid Mixtures, by Arne Tiselius. (4) Spread Monolayers of Protein, by Henry B. Bull. (5) Films of Protein in Biological Process, by Alexander Rothen. (6) The Chemical Determination of Proteins, by Paul L. Kirk. (7) Reactions of Native Proteins With Chemical Reagents, by Roger M. Herriott. (8) The Amino Acid Requirements of Man, by Anthony A. Albanese. (9) The Use of Protein and Protein Hydrolyzates for Intravenous Alimentation, by

Robert Elman. (10) The Preparation and Criteria of Purity of the Amino Acids, by Max S. Dunn and Louis B. Rockland. (11) The Plasma Proteins and Their Fractionation, by John T. Edsall.

This 3rd annual volume maintains the same high degree of excellence observed in the earlier issues.

H. V.

THE ACUTE INFECTIOUS FEVERS. By ALEXANDER JOE, M.D., D.S.C., Univ. of Edinburgh. Pp. 276; 64 ills. Phila.: Blakiston, 1947. Price, \$4.50.

THE expressed purpose of this book is to present the personal experience of the author to the beginners in the field of infectious diseases. The common contagious diseases, puerperal sepsis, cerebral spinal fever, enteric fever, erythema infectiosum and serum reactions are discussed.

Adequate description of the symptoms, pathology, etiology and complications are presented. Detailed nursing and supportive care is presented in each chapter. This should aid in comforting the patient. The author has evidently mastered this phase of the art of therapy. However, the description of the newer antibiotics is inadequate. Although sulfonamides are recommended for 7 of the 13 diseases, the toxic reactions to these drugs are briefly mentioned and only once, in the sixth chapter. The index does not refer to sulfonamide toxicity. Penicillin is mentioned briefly but the author fails to prescribe it in the therapy of agranulocytosis. The value of penicillin in the treatment of puerperal fever is regarded as subjudice; yet the author advises the intrauterine instillation of glycerine in this condition. To the reviewer, this seems to be a dangerous practice. Streptomycin is not mentioned in the book. The adrenal extract therapy in the Waterhouse-Fridericksen syndrome is not discussed. The use of anti-histamine medication in combating penicillin and serum reactions is not mentioned.

No bibliography is presented.

In a field in which therapeutics is rapidly changing, a complete treatise should contain the experience of a seasoned clinician plus the recent discoveries of the research worker. The scope of this book adequately presents the former but not the latter.

M. P.

FUNCTIONAL CARDIOVASCULAR DISEASE. By MEYER FRIEDMAN, M.D., Lt. Col. Med. Res. Corps, U.S.A.; Director Harold Brunn Inst. for Cardiovascular Research, Mt. Zion Hosp.; etc. Pp. 266; 24 tables. Balt.: Williams & Wilkins, 1947. Price, \$3.00.

THIS book represents the effort of an internist trained in cardiovascular dynamics and clinical medicine to deal with the subject commonly spoken of as neurocirculatory asthenia "by filling in the physiological gaps between the concept of the disease held by the internist and that held by the psychiatrist." In other words, physiological reactions have been sought to explain the occurrence of the various phenomena arising in this disorder. The author has gone a step further than the usual medical approach to this subject both from the physiological and psychological standpoint. In spite of some valuable physiological and clinical observations on the mechanism of pain, the pathogenesis of giddiness and the introduction of new concepts of the pathogenesis of the total disorder, it is doubtful if the study brings us much closer to an understanding of this complicated problem. The use of a new terminology—cortico-hypothalamic imbalance, cortical recession, etc., seems unfortunate. Apparently, the author has developed his own psychological approach in trying to understand and treat the acute and chronic sufferers from this disorder, and, when he is asked why the Function Cardiovascular Disease syndrome should not be called "anxiety neurosis," he can find no objection if "it is realized that many so-called cases of anxiety neurosis are probably not due to anxiety." This would seem to represent a pit-fall of the clinical observer untrained in psychodynamics. Finding the source of anxiety in anxiety neurosis depends upon the psychological training and experience of the observer. As Ewing said about the microscope as an instrument of precision, "It all depends on who is looking through it." Similar criticism might be made concerning the psychotherapy developed by the author; but in spite of an obvious lack of training in this field he has made some shrewd and helpful observations.

These criticisms, however, should not detract from the many interesting and valuable observations contained in this careful study, which can be highly recommended

both to internists and psychiatrists. The former will gain a better appreciation of emotional factors and the latter will benefit from the careful scientific discipline demonstrated by the author's approach.

E. W.

NUTRITIONAL AND VITAMIN THERAPY IN GENERAL PRACTICE. By EDGAR S. GORDON, M.D., Ph.D., Assoc. Prof. of Medicine, Univ. of Wisconsin. 3d ed. Pp. 410. Chicago: Year Book Publishers, 1947. Price, \$5.00.

DR. GORDON has written a comprehensive survey of available information in the nutrition field. Included are chapters on all of the vitamins, on minerals, protein, fat and carbohydrate. There is also a chapter on weight control, one on dental problems in nutrition and a final chapter dealing with the economic side of nutrition. Under every heading, is a brief historical background, a simple statement of the chemistry and physiology fundamental to an adequate understanding of the rôle of the dietary component in question with practical consideration of the therapeutic indications for, and ways of handling intelligently, the clinical administration of each nutrient. The text is well documented by references, food tables, a list of available commercial preparations, and a brief summary of laboratory methods of dosage for deficiency diseases. The result is a volume useful both to the student of nutrition and to the clinician.

K. E.

GASTRITIS. By RUDOLPH SCHINDLER, M.D., F.A.C.P., Clinical Prof. of Internal Medicine (Gastroenterology), College of Medical Evangelists, Los Angeles, Cal.: Pp. 462; 96 ills., 2 color plates. New York: Grune & Stratton, 1947. Price, \$10.00.

A BOOK that comprises a complete treatise on the subject of gastritis, it contains chapters on history, definitions used, classifications, gross and microscopic pathology, clinical considerations (etiology, symptoms, diagnosis, course, prognosis and treatment), concomittant diseases and sequellæ of gastritis. In addition there is a chapter devoted to gastritis in Military Medicine. Fifty-five selected cases of gastritis are summarized. There is an excellent bibliography of 401 references.

The subject matter on a rather controversial disease is clearly presented by one of the leading authorities in the field of gastroscopy. The author draws freely on a very large personal experience but also presents opinions and experiences of others. Not any of the phases dealing with the subject are neglected. A close correlation between gastroscopic and microscopic findings is established. There are 89 large reproductions of photomicrographs of tissue sections, 4 photographs of gross specimens, and 2 color plates that present 12 gastroscopic pictures of normal mucosa, chronic gastritis, tumor forming gastritis and atrophic gastritis with carcinoma. These add greatly to the value of the book, which reads easily, is well written and brings the subject matter up to date. It may be read with profit by internists as well as specialists in the field.

T. M.

THE PSYCHOANALYTIC STUDY OF THE CHILD.

Volume II. Editorial Board (United States): PHYLLIS GREENACRE, M.D., HEINZ HARTMANN, M.D., *et al.* Great Britain: ANNA FREUD, WILLIE HOFFER, M.D., Ph.D., L.R.C.P., EDWARD GLOVER, M.D. Pp. 424; 6 tables. New York: Internat. Univ. Press., 1946. Price, \$7.50.

An illustrative method of treatment is found in the Analysis of a Case of Night Terror, about a boy who, having witnessed sexual relations between quarrelsome parents, regarded his father's performances as sadistic and developed a sympathetic affection for his mother. Soon amorous feelings for the analyst were experienced and exposure of his person followed. Secretly observing other children having sexual relations led to masturbation, and immature desire induced a proposal of marriage to his analyst. Psychoanalytic interviews of about a year and a half gave relief from night terror and general improvement. At about 14 he passed through normal puberty.

Though psychiatrists of the eighteenth and nineteenth centuries knew disturbed emotions could lead to neuroses, they were not aware of conflicts. However, J. B. Felix Descuret, a French physician, realized their significance as a cause of psychosomatic symptoms. Among other interesting topics discussed are The Child's Laughter, Twins, and a Case of Superego Deterioration.

N. Y.

MANUAL DE DERMATOLOGIA. Editado bajo los auspicios del Comité Médico de la división de Ciencias Médicas del "National Research Council." Por DONALD M. PILLSBURY, M.D., MARION B. SULZBERGER, M.D., CLARENCE S. LIVINGOOD, M.D. Translated by ROBERTO QUERO, M.D. Pp. 470; 108 ills. Havana, Cuba: Publicaciones Científicas (M. V. Fresneda, Ed.), 1947. Price not given.

THIS volume is the Spanish rendition of the popular MANUAL OF DERMATOLOGY (Saunders, Philadelphia, 1942), reviewed in this Journal, March, 1943, Vol. 205. The translator has stuck faithfully to the American text and the publishers have dressed up the physical appearance of the book by the addition of a two-toned cover and a convenient thumb-mark to the appendix. The page and type size of the translation are somewhat larger than those of the American edition. This edition extends to the Latin American countries the usefulness of an already widely accepted book.

II. B.

PSYCHIATRIC RESEARCH. Papers Read at the Dedication of the Laboratory for Biochemical Research, McLean Hosp., Waverly, Mass. By CECIL K. DRINKER, JORDI FOLCH, STANLEY COBB, HERBERT S. GASSER, WILDER PENFIELD and EDWARD A. STRECKER. Pp. 113; 7 ills. (Harvard Univ. Monograph in Medicine and Public Health, No. 9). Cambridge: Harvard Univ. Press, 1947. Price, \$2.00.

THIS series of addresses at McLean Hospital is opened by a history of research at that hospital written by Cecil Drinker. A survey, by Jordi Folch, of the chemical brain follows, in which are listed the brain's lack of a lymphatic system, its abundant blood supply, its very high oxygen consumption, its specialized metabolism with a unique chemical composition and a blood-brain barrier. Stanley Cobb describes the applications of research techniques to patients at the Massachusetts General Hospital. Herbert Gasser advances the suggestive statement that the most significant contribution to biology within the span of his lifetime is the elucidation of the steps in intermediary metabolism. Edward Strecker, emphasizing the importance of psychiatric research, states his conviction that the exact sciences need

less-exact psychiatry to save man from destroying himself. Wilder Penfield describes the research possibilities in a study of psychological seizures. E. B.

MEDICAL CLINICS OF NORTH AMERICA.

March 1947. Nationwide Number. *Symposium on Diabetes*. Pp. 259-495. Phila.: W. B. Saunders. Price, \$16.00 a year.

THIS symposium on diabetes is a useful summary of current concepts of this disease. Although the papers might have been arranged in a somewhat more effective order, the material in them should interest physicians in the field of Internal Medicine. Some of the laboratory aspects are discussed by Drs. Lawrence, Mosenthal and Marble. Methods of handling various clinical problems are described by Drs. Boyd, White, Sprague, Root, Brigham, Duncan, Ling and Rynearson. The modern preparations of insulin and their uses are discussed by Drs. Colwell, Peck and Goldner. The collection is rounded out by Drs. Striker, Wilkerson, Bailey and White and Mr. Herbert Marks who summarize past progress and indicate trends of current and future work.

One of the most interesting aspects of the symposium as a whole is the attitude of the various writers concerning the degree of control of the diabetes and the goal of therapy. With the recent enthusiasm on the part of some writers for a regimen which allows glycosuria and elevated blood sugars as long as the patient feels well and is clinically in good condition, there has been a tendency on the part of many doctors to feel that they can safely relax the older, more rigid standards. It is interesting to see, however, that this group of experienced men from different parts of the country, writing on different aspects of diabetes, agree on the advisability of maintaining blood sugar levels within normal limits and keeping glycosuria at a minimum.

The sections on the interpretation of Glucose Tolerance Curves and the Melliturias should be of practical value to the physician confronted with a borderline case. Although there is nothing very new presented in the papers on insulin, they do give an adequate and useful summary of the available preparations, their activities and the indications for each. The physiology, pathology and treatment of the complications of diabetes as well as acidosis and

coma are ably discussed. Dr. White's observations on pregnancy complicating diabetes of long duration are of particular importance in view of the increasing number of childhood diabetics now reaching the child-bearing age.

Although the protagonists of free diet are not represented, the symposium will give the general practitioner a fair view of the opinions of the majority of specialists in diabetes. H. C.

SYNOPSIS OF OPERATIVE SURGERY. By H. E. MOBLEY, M.D., F.A.C.S., Chief of Surgery, St. Antony's Hosp., Morrilton, Ark. 2nd ed. Pp. 416; 383 ill., 37 in color. St. Louis: C. V. Mosby, 1947. Price, \$6.00.

IN this book an attempt is made to show and describe the essential steps of all the common operations of general surgery and the specialties, neurosurgery, urology, orthopedics, gynecology and otolaryngology. "It is the author's hope that the fundamental principles of operative technique presented will give the student the desired information without extensive research on his part."

Discussion of preoperative and postoperative care and anesthesia in the first 3 chapters will seem inadequate to the present-day medical student, and some statements will be surprising, *e. g.*, "Adrenalin chloride heads the list of drugs to combat shock." In the next 3 chapters there are general remarks about surgical technique, knot-tying and suturing, and incisions. Some inadvisable incisions are shown, *e. g.*, longitudinal incisions across flexion creases. In the rest of the book operations on the various regions of the body are described and illustrated. For the most part, sound and well-established procedures have been chosen, and the descriptions are clear and accurate. To the novice the small size of the illustrations and the omission of some steps may be a handicap. Indications for operations are mentioned briefly, if at all, and in some instances, such as the recommendation for local excision of non-obstructing gastric ulcer, are not in agreement with current surgical teaching. Also, few will agree with the statement that the injection treatment of inguinal hernia gives "results as good or better than those of the operation." Busy students, however,

desiring ready access to essential details of operative surgery, will doubtless find this book useful.

C. K.

VITAMINS AND HORMONES. Advances in Research and Applications. Edited by ROBERT S. HARRIS and KENNETH V. THIMAN. Vol. IV. Pp. 406. New York: Academic Press, 1947. Price, \$6.80.

The following subjects are reviewed: The Newer Hematopoietic Factors of the Vitamin B Complex, by J. J. Pflüger and A. G. Hogan; Nutrition and Resistance to Infection: The Strategic Situation, by H. A. Schneider; Manifestations of Nutritional Deficiency in Infants, by F. W. Clements; Effect of B Vitamins on the Endocrinological Aspects of Reproduction, by Roy Hertz; Nutritional Therapy of Endocrine Disturbances, by M. S. Biskind; The Thyroid and Diabetes, by B. A. Houssay; Thyroactive Iodinated Proteins, by E. P. Reineke; The Protein Anabolic Effects of Steroid Hormones, by C. D. Kochakian; Methods of Bioassay of Animal Hormones, by S. A. Thayer.

As in previous volumes the subjects are well covered by authors familiar with their respective fields. The author of the second chapter has deviated somewhat from the customary type of scientific review in that the discussion is more philosophic. In the Reviewer's opinion this departure is a pleasant interlude from the usual recitation of facts and observations, even though it may not so well answer the needs of the scientific investigator.

There are several minor errors, either typographic or otherwise. Some of these are found on pages 93, 168, 271, 320, 338 and 354. On page 200 the reader is informed that 9 out of 19 equals 52%. These are all minor and can easily be overlooked.

This volume includes a cumulative index, both author and subject, for the first 4 volumes.

J. J.

changed flint-lock to punch locks, carried on research in chemistry and discovered chloroform. The little volume, well illustrated and documented, is of interest to medical historians and to specialists in anesthesiology. It serves the purpose of bringing together data about a little known man whose accomplishments in the scientific world have been recognized only relatively recently.

R. D.

EXPERIENCES WITH FOLIC ACID. By TOM D. SPIES. Pp. 110; 34 figs. Chicago: The Year Book Publishers, 1947. Price, \$3.75.

This small monograph is principally a summary of observations on the clinical use of folic acid made at Cincinnati, Ohio, Birmingham, Ala., Havana, Cuba, and San Juan, Puerto Rico, by Dr. Spies and his associates. Two of these medical centers are located in the temperate zone where pernicious anemia is common and sprue is uncommon; the other 2 in the tropical zone where the opposite is the case. This arrangement afforded an opportunity to study the effect of folic acid on both of these diseases which are characterized by a macrocytic anemia.

In addition to giving some of the results, the methods of approach are also outlined in full, including the routine of handling the patients. The main conclusions are: (1) Folic acid (pteroylglutamic acid) is very effective in treating nutritional macrocytic anemia, sprue, the anemia of pellagra and the macrocytic anemia of pregnancy. (2) Folic acid is very beneficial in the treatment of pernicious anemia and will correct the blood dyscrasia, but the neurologic signs, which frequently occur in pernicious anemia, were not prevented or cured. In this respect folic acid is not so beneficial as liver extract. (3) The daily dose of folic acid, either parenterally or orally is 10 to 20 mg. J. J.

DR. SAMUEL GUTHRIE, DISCOVERER OF CHLOROFORM. By J. R. PAWLING, M.D. Pp. 122; 26 ill. Watertown, N. Y.: Brewster Press, 1947. Price, \$3.50.

This is the story of a physician who settled in upper New York State in 1817, erected a gun-powder mill, a distillery, a chemical laboratory; manufactured gunpowder, and

THERAPEUTIC EXERCISE. By F. H. EWERHARDT, M.D., and GERTRUDE F. RIDDLE, B.S.R.N., R.P.T. Pp. 152. Phila.: Lea & Febiger, 1947. Price, \$2.50.

This concise manual, with its clear definitions, will be useful to all those who work in the Orthopedic field. Joint motion graphs

and notations on methods of muscle testings aid in presenting a clear picture of muscle participation in joint movements. There is a good chapter explaining muscle contraction with the effect of artificial stimuli by various agents. Applicable treatment and exercise for weak lower back, abdominal muscle weakness and flat feet are considered. Treatment for various diseases of the heart, hemiplegia, injuries to the seventh nerve, arthritis, tabes dorsalis and respiratory cases are other things touched upon. The causes and treatments of poliomyelitis are discussed at length, with indications for administration of hot packs, together with an evaluation of muscle spasm. Muscle re-education in poliomyelitis is emphasized as the chief part of the treatment. A valuable study of the spastic child not only includes clinical findings but a well-rounded program for medical treatment including Physiotherapy and Occupational Therapy. This book is a comprehensive presentation; however, it would be interesting and valuable to have had more of the Occupational Therapist's point of view on many items of treatment.

V. C.

GENETICS, MEDICINE, AND MAN. By H. J. MULLER, Indiana University, and C. C. LITTLE, Roscoe B. Jackson Memorial Laboratory, and H. SNYDER, Ohio State Univ. Pp. 158; 29 figs. Ithaca, N. Y.: Cornell Univ. Press, 1947. Price, \$2.25.

In language easily understood, the chapters on Genetic Fundamentals discuss the present-day concepts of the principles of heredity, of the relation of the gene to the organism, to sexual reproduction, and the "causes that have led to its ascendancy among higher living things." Sections on Parental Influence and Growth and Individuality deal with the recognized parenteral factors that may affect the offspring biologically. Due credit is given to the knowledge gained through controlled experiments on laboratory mammals.

It is shown how Human Heredity and the Mutant Gene in Man have now sufficiently entered the realm of scientific knowledge so that sound advice may be given toward the prevention of disease and the solving of some medico-legal problems. Concerning the Rh blood types, the authors state that recent investigations "have indicated that the lack of oxygen caused by the destruction

of the embryo's erythrocytes may cause mental deficiency" and add: "It would seem to be a wise precaution for every woman entering upon marriage to consult her physician in regard to her Rh type of blood."

Another interesting observation cited is that through the study of electroencephalograms, Lennox and his associates have found that 1 or both parents of an epileptic usually shows cerebral dysrhythmia, if not epilepsy. The existence of such recordings may make it possible to determine whether or not normal persons of an epileptic family can transmit the underlying gene. Many other complex hereditary and environmental influences receive careful scientific consideration in this small book.

N. Y.

AN INTRODUCTION TO BACTERIOLOGICAL CHEMISTRY. By C. G. ANDERSON, Ph.D., Wellcome Physiological Research Laboratories, Beckenham, Kent, England. 2nd ed. Pp. 500; 34 tables; 11 figs. Baltimore: Williams & Wilkins, 1946. Price, \$5.00.

THE 1st edition of this book, which was well received, has been improved by the inclusion of chapters on Antibiotics and Growth Factors. By the addition to chapter endings of references to reviews and monographs its usefulness has been enhanced.

In early texts on bacteriology one often found a discussion of the question of the plant and animal nature of bacteria. It was thought, when the chemistry of nucleic acids was being studied and the plant nucleic acids were supposed to be different from animal nucleic acids, that a knowledge of the bacterial nucleic acids would aid in distinguishing the plant or animal characteristics of bacteria. Again the early question of the presence of nuclei in bacterial cells was also to be solved by studying the nucleic acids, which were the characteristic constituents of the nucleus. Since 1936, however, both of these expectations were frustrated when Caspersen showed that nucleic acids were found in both the nucleus and cytoplasm, and others have found that both types of nucleic acids are found in the same cell. In fact, in the liver more than 3 times the quantity of the so-called plant type than of the animal type has been reported.

It is disappointing to find that the author on page 332 describes the nucleic acids as being made up of nucleotides of "2 main types (a) those derived from yeasts and

plants and (b) those derived from animals." Although some of his latter references refer to "animal or desoxyribonucleic acid" and "plant or ribonucleic acid," no mention is made of the present-day knowledge that both types do occur in the same animal cell. Again, on page 60, one finds it difficult to understand the meaning of "on hydrolysis those (nucleoproteins) of the tubercle bacillus give a mixture of the pyrimidine and purine types of nucleic acid, but those of most other bacteria give the purine type only." Such a division of nucleic acids is unknown so far as one can find in the most authoritative sources. J. S.

A HISTORY OF SCIENTIFIC ENGLISH. The Story of its Evolution Based on a Study of Biomedical Terminology. By EDMUND ANDREWS, M.D. Pp. 342; 18 figs. New York: Richard R. Smith, 1947. Price, \$7.50.

SCIENTISTS, and particularly American scientists, are often reproached, and with some justice, for the imperfections of form in which their scientific presentations are couched. At the basis of many of the barbarisms, or obscure or even misleading statements, is an ignorance of the true meanings of the words used, which naturally links itself with inability to express shades of exact meaning so important in scientific writing. For all such writers, this book, the last work of a brilliant surgeon and philologist who died when only 48 years old, can be a veritable *vade mecum*, providing a wealth of practical information and many explanations of the evolution of scientific nomenclature. For some it will go much further, stimulating an interest in words, their derivations and their meanings that may constitute a permanent intellectual satisfaction.

E. K.

NEW BOOKS

Cornell Conferences on Therapy. Vol. II. Edited by HARRY GOLD, M.D., et al. Pp. 354. New York: The Macmillan Co., 1947. Price, \$3.75.

A Neuro-Vascular Syndrome Related to Vitamin Deficiency. By HENDRIK SMIT-SKAMP. Pp. 114. Amsterdam: Scheltema & Holkema, 1947. No price given.

Zeitschrift für Vitamin-, Hormon- und Fermentforschung. Von EMIL ABDERHALDEN. I Band, Heft 1 und 2. Pp. 215. Wien: Urban & Schwarzenberg; New York: Grune & Stratton, 1947. Price, \$20.00 a year.

History of Medicine. By CECILIA C. METTLER, Ph.D., Late Ass't Prof. of Medical History, Univ. of Georgia. Pp. 1215; 16 ills. Philadelphia: Blakiston, 1947. Price, \$8.50.

George Crile, an Autobiography. Edited by GRACE CRILE. In 2 vols. Pp. 624; 22 ills. Philadelphia: J. B. Lippincott, 1947. Price, \$10.00.

The Thematic Apperception Test. By SILVAN S. TOMKINS, Ph.D. With the Collaboration of ELIZABETH J. TOMKINS, B.A. Pp. 297. New York: Grune & Stratton, 1947. Price, \$5.00.

Conference on Metabolic Aspects of Convalescence. Edited by EDWARD C. REIFENSTEIN, JR., M.D. Transactions of the 13th and 14th Meetings. Pp. 232 and 190; 67 and 78 figs. New York: Josiah Macy, Jr. Foundation, 1947. Price, \$2.00 a copy.

Neutron Effects on Animals. By the STAFF OF THE BIOCHEMICAL RESEARCH FOUNDATION, Newark, Delaware, ELLICE McDONALD, M.D., Director. Pp. 198; 29 ills. Baltimore: Williams & Wilkins, 1947. Price, \$3.00.

Dr. Kirkbride and His Mental Hospital. By EARL D. BOND, M.D. Pp. 162; 7 ills. Philadelphia: J. B. Lippincott, 1947. Price, \$3.50.

The Practical Nurse. By DOROTHY DEMING, R.N., Consultant in Public Health Nursing. Pp. 370. New York: The Commonwealth Fund, 1947. Price, \$3.00.

Spezifische Typhustherapie. Von DOZENT DR. FERDINAND NAGL und DR. OSEAR LACHNER. Pp. 63; 32 figs. Wien: Wilhelm Maudrich; New York: Grune & Stratton, 1947. Price, \$2.20.

Osteophthisis Pelvis et Femorum. Von DR. GOTTFRIED HARTMANN. Pp. 183; 19 ills. Wien: Wilhelm Maudrich; New York: Grune & Stratton, 1947. Price, \$5.00.

Ear, Nose and Throat. By GEORGE D. WOLF, M.D., Ass't Clinical Prof. of Otolaryngology, New York Medical College. Pp. 523; 149 ills., 25 with color. Philadelphia: J. B. Lippincott, 1947. Price, \$10.00.

The Metropolitan Life. By MARQUIS JAMES: Pp. 480; 33 ills. New York: The Viking Press, 1947. Price, \$5.00.

Essentials of Pharmacology. By FRANCES K. OLDHAM, M.Sc., Ph.D., F. E. KELSEY, Ph.D., and E. M. K. GEILING, Ph.D., M.D., Distinguished Service Professor and Chairman of the Department of Pharmacology, the Univ. of Chicago. Pp. 440; 5 ills. Philadelphia: J. B. Lippincott, 1947. Price, \$5.00.

THIS volume presents an adequate outline of pharmacology, including discussion of numerous agents quite recently introduced. The reader who seeks a more complete description of drug action or an examination of the basic physiology and biochemistry of rational therapy is, however, likely to be disappointed. It should make a useful textbook for nurses, dental students, pharmacists and others who desire an accurate and up-to-date bird's-eye view of pharmacology. S. K.

A Concise Comparative Anatomy. By WILLIAM HENRY ATWOOD. Pp. 413; 303 ills. St. Louis, Mo.: C. V. Mosby, 1947. Price, \$3.75.

Stereoscopic Atlas of Neuroanatomy. By H. S. RUBINSTEIN, M.D., Ph.D., Director, Alfred Ullman Laboratory for Neuropsychiatric Research, Baltimore, and C. L. DAVIS, M.D., Prof. of Anatomy, Univ. of Maryland. Pp. 20; 43 ills. New York: Grune & Stratton, 1947. Price, \$10.00.

Beiträge zur Kenntnis der Blutgerinnung. Von W. K. RIEBEN. Pp. 96; 26 ills. Basel: Benno Schwabe & Co., 1947. Price, Geb. fr., 9.

Hodgkin's Disease and Allied Disorders. By HENRY JACKSON, JR., M.D., Ass't Prof. of Medicine, Harvard Medical School, and FREDERIC PARKER, JR., M.D., Assoc. Prof. of Pathology, Harvard Medical School. Pp. 177; 14 plates. New York: Oxford University Press, 1947. Price, \$6.50.

Endogeneous Endocrinotherapy Including the Causal Cure of Cancer Compendium. By DR. JULES SAMUELS. Pp. 539. Amsterdam, Holland: Holdert & Co., 1947. No price given.

Diagnosis in Daily Practice. By BENJAMIN V. WHITE, M.D., Ass't Clinical Prof. of Medicine, Yale Univ., and CHARLES F. GESCHICKTER, M.D., Prof. of Pathology, Georgetown Univ. Pp. 693; 360 ills. Philadelphia and London: J. B. Lippincott, 1947. Price, \$15.00.

Fundamentals of Neurology. By ERNEST GARDNER, M.D., Ass't Prof. of Anatomy, Wayne Univ., Detroit. Pp. 336; 133 ills. Philadelphia and London: W. B. Saunders, 1947. Price, \$4.75.

ANY book which attempts to clarify for the beginner the mysteries of the nervous system must be approached with anticipation and welcome. No task could be more difficult or require more courage. It is inevitable that some subjects be sacrificed to the importance of others. Gardner has performed a useful task in this little volume. He approaches his subject from a somewhat different angle than others who have written on similar subjects. The book covers the subject quite adequately and can be recommended for medical students and all those who seek an authoritative background in neurology. B A.

NEW EDITIONS

Diagnostic Bacteriology. By ISABELLE GILBERT SCHAUB, A.B., and M. KATHLEEN FOLEY, A.B. 3d ed. Pp. 532. St. Louis: C. V. Mosby, 1947. Price, \$4.50.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Prof. of Bacteriology, Indiana Univ. 4th ed. Pp. 603; 126 ills. Philadelphia and London: W. B. Saunders, 1947. Price, \$6.50.

Pharmaceutical Arithmetic. By IGNATIUS J. BELLAFIORE, Ass't Prof. of Pharmacy, St. John's Univ. College of Pharmacy, Brooklyn. 2d ed. Pp. 395. St. Louis: C. V. Mosby, 1947. Price, \$3.75.

Penicillin Therapy. By J. R. GOYAL. 2d ed. Pp. 177. Delhi, India: Medical Review of Reviews, 1947. No price given.

Physical Medicine in General Practice. By WILLIAM BIERMAN, M.D. With a Chapter on Medical Rehabilitation by SIDNEY LIEHT, M.D. 2d ed. Pp. 686; 310 ills. New York: Paul B. Hoeber, 1947. Price, \$8.00.

Textbook of Zoology. By GEORGE EDWIN POTTER, Ph.D., Prof. of Zoology, Agricultural and Mechanical College of Texas. 2d ed. Pp. 948; 445 figs. St. Louis: C. V. Mosby, 1947. Price, \$5.00.

THIS edition includes revision of several chapters and a new section on Mammalian Development. It represents a combination of type material (555 pages) with chapters on Regeneration, Parasitism, Comparative Embryology, Biological Effects of Radiation, *et cetera*, written by specialists. A glossary, bibliography and exceptionally clear illustrations directly labelled add much to the value of the book.

Practical Clinical Psychiatry. By EDWARD A. STRECKER, M.D., FRANKLIN G. EBAUGH, M.D., and JACK R. EWALT, M.D. With Section on *Psychopathologic Problems of Childhood.* By LEO KANNER, M.D. 6th ed. Pp. 476; 35 ills. Philadelphia: Blakiston, 1947. Price, \$5.00.

In this sixth edition, a psychiatric textbook record, new chapters will be found on Traumatic Reactions, Psychosomatic Medicine and Pathological Drinking. Earlier chapters are rewritten under the heading Personality Development. Such changes leave this the best single book on psychiatry for the medical student and the general physician, and a reference source for the psychiatrist. E. B.

An Atlas of Anatomy. By J. C. BOILEAU GRANT, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Prof. of Anatomy, Univ. of Toronto. 2d ed. Pp. 496; 591 ills. Baltimore: Williams & Wilkins, 1947. Price, \$10.00.

Recent Advances in Medicine. By G. E. BEAUMONT, D.M., F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital, etc., and E. C. DODDS, M.V.O., M.D., F.R.C.P., F.R.I.C., F.R.S. (Edin.), Prof. of Biochemistry, Univ. of London, etc. 12th ed. Pp. 422, 42 ills. Philadelphia: Blakiston, 1947. Price, \$6.00.

THE subject matter is fairly complete and presented clearly and concisely. Adequate emphasis is placed on physiological and biological principles, but theoretical discussion is largely avoided. This book is recommended for those practitioners who have not had opportunity for recent post-graduate study. A good bibliography is given at the end of each chapter R. K.

Artificial Pneumothorax in Pulmonary Tuberculosis. By T. G. HEATON, M.B., Chest Clinician, Toronto Western Hospital. 2d ed. Pp. 292. Toronto: The Macmillan Co., 1947. Price, \$4.50.

Illustrations of Regional Anatomy. By E. B. JAMESON, M.D., Senior Demonstrator and Lecturer Emeritus, Anatomy Department, Univ. of Edinburgh. 7th ed. 320 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$20.00.

THIS series consists of a 7 volume atlas composed solely of illustrations without accompanying text. Each volume takes up a major region of the body such as thorax, abdomen, lower extremity, *et cetera*, picturing all systems in the given region. The illustrations are well done. They are printed on glossy paper, are attractively colored, and are simple and clear. Unnecessary detail is omitted. This set should be useful to the student of surgery and as a laboratory manual at the dissecting table. A. R.

Fundamentals of Clinical Neurology. By H. HOUSTON MERRITT, M.D., FRED A. METTLER, M.D., and TRACY JACKSON PUTNAM, M.D. Pp. 289; 96 ills. Philadelphia: Blakiston, 1947. Price, \$6.00.

THE three authors contribute clinical, anatomical and physiological sections. It has the advantage of some of the beautiful illustrations taken from Dr. Mettler's larger *Neuroanatomy*. The plan of the book is a succinct review of applied anatomy and physiology and the briefest discussion of clinical disorders. It should serve as an admirable introduction to students and as a review for more experienced practitioners. One might suggest that a somewhat clearer distinction be made between the physiology that has been worked out upon animals and that upon man. The book should serve as an admirable outline for teaching. G. G.

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ORIGINAL ARTICLES

RESULTS OF PROLONGED MEDICAL TREATMENT OF HYPERTHYROIDISM WITH THIOUREA*

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To determine the efficacy and advisability of prolonged medical treatment of thyroid overactivity, all hyperthyroid patients seen by the Metabolism Department of the New Haven Hospital and Dispensary during the past 3 years have been given thiourea, usually together with strong solution of iodine. This antithyroid drug was used because initial trials indicated that it is not only at least as effective as thiouracil but also less toxic.^{1,2} The results of this treatment analyzed in this paper and compared with those obtained with other therapeutic measures indicate that control of hyperthyroidism is possible for long periods of time in most patients.

Material's and Methods. Of 118 patients studied, the average age was 45.4 years. More than four-fifths of the patients were

between 20 and 60 years of age. The oldest patient treated was 79 and the youngest 16. Females outnumbered males 4 to 1.

The diagnosis of hyperthyroidism was based on the clinical history and physical findings, the level of the basal metabolic rate and the concentration of precipitable or hormonal iodine in serum. This last measurement^{7,11} has proved to be a particularly sensitive index in the diagnosis of thyroid overactivity. In hyperthyroidism the serum precipitable iodine is greater than 8 gamma per 100 cc., and in hypothyroidism less than 4 gamma per 100 cc.¹⁵ In 16 of the patients recurrent hyperthyroidism followed previous thyroidectomies. An isolated adenoma was noted in 7 of the 118 patients of the group. In the others the glands were diffusely enlarged, with or without nodulation. Exophthalmos or other eye signs such as stare or widened palpebral fissures were observed in more than a third of the subjects. Auricular

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† Formerly Assistant Professor of Medicine, Yale School of Medicine.

‡ Deceased June 26, 1947.

fibrillation replaced the sinus mechanism in 7 instances, and signs of congestive failure, *i. e.*, râles with or without edema, were found in 12 of the group before treatment.

The therapeutic regimen with respect to the size of the daily dose of thiourea and the concomitant use of strong solution of iodine was varied at intervals in each patient, so that appropriate principles of therapy could be evolved. Treatment was limited to thiourea alone in 20 of the patients. The other 98 were given 5 to 15 drops of strong solution of iodine daily prior to, or at the time of, administration of thiourea and continued to take it throughout the course of treatment. The daily intake of thiourea ranged between 280 and 15 mg. but remained constant in any particular patient during periods of at least 6 weeks. In most patients, however, the dosage of the drug was reduced following the appearance of remission. During the first few weeks of therapy, and thereafter as necessary, the clinical states of the patients were checked at intervals with examinations of the urine, the formed elements of the blood, and measurements of the basal metabolic rate and serum precipitable iodine.

Of the 118 patients who were started on a medical regimen to control thyroid overactivity, 11 have been treated for 2 years or longer, 46 for 1 to 2 years and 32 others for 6 to 12 months. Twenty-nine subjects have received thiourea for less than $\frac{1}{2}$ year. These 29 are not included in summarizing the results on the 89 patients followed during periods of 6 months to more than 2 years.

Eighteen of the original 118 patients are no longer under observation; 12 voluntarily

stopped treatment; 3 moved beyond commuting distance; 3 died during the course of treatment. Patient B54264, a 42 year old female, died of malnutrition secondary to hyperthyroidism which responded initially to treatment and relapsed when the patient decreased and discontinued the intake of drugs. The other 2 patients, B34401 and PC2473, died of ulcerative colitis and pulmonary infarction respectively. The remaining 100 patients continue visits at intervals of 4 to 12 weeks.

RESULTS. Effects of Thiourea Administration. The response to therapy has on the whole been satisfactory. From Table 1 which contains data on 89 cases treated 6 months or longer, it is evident that the progressive weight loss which characterized the hyperthyroid state in 87% of the patients was either checked or, more often, replaced by weight gain. The increase in body weight ranged from 2 to 22.5 kg., with 3.5 as the average. The pulse decreased to 90 per minute or lower in all but 7% of the patients. The rate before treatment in the group as a whole averaged 94 per minute. The average at 6 or more months of treatment was 76 per minute. The basal metabolic rate for the group was +39% before treatment and declined to less than +20% in 4 out of every 5 cases treated, with an average of +10% following medical therapy. However, with a combination of these different criteria there were 23 patients whose hyper-

TABLE 1.—STATUS OF 89 HYPERTHYROID PATIENTS BEFORE AND AFTER TREATMENT WITH THIOUREA FOR 6 MONTHS OR LONGER

	Before treatment (% of cases)	After treatment* (% of cases)
Body weight:		
Constant or increasing	13	13
Decreasing	87	17
Pulse rate:		
66 to 90 per minute	56	93
91 to 144 per minute	44	7
Basal metabolic rate:		
Less than +21%	16	80
Greater than +20%	84	20
Serum precipitable iodine:		
Less than 8 gamma per 100 cc.	0	60
Greater than 7.9 gamma per 100 cc.	100	40†

* Six months or more of treatment.

† In only 10% of the 66 patients whose hyperthyroidism appeared to be controlled by thiourea were the serum precipitable iodines above euthyroid levels (see "results").

thyroidism was only partially controlled by thiourea. Two did not follow medication faithfully; 15 were on small doses of thiourea, only up to 100 mg. daily (4 on 25 q.d.; 3 on 25 b.i.d.; 7 on 25 t.i.d. and 1 on 50 mg. b.i.d.). Three had been pregnant, and following delivery regulation of thyroid overactivity had to be modified. Three on 70 mg. of thiourea b.i.d. or t.i.d. had basal metabolic rates between +27 and +35%, but their pulses ranged from 72 only up to 84. Of these, the weight of 1 was increasing, of 1 was constant and of 1 was decreasing.

At the time the diagnosis of hyperthyroidism was made the values of the serum precipitable or hormonal iodine ranged from 8.1 to 27, averaging 12.7 gamma. With treatment the serum precipitable iodine decreased toward or to normal in 83% of the patients.

Following 6 or more months of therapy with thiourea 53 patients had serum precipitable iodines below 8 and 36 serum precipitable iodines above 7.9 gamma. Only 1 of these iodines above 8 gamma is an exception to the rule that euthyroid levels of serum iodine occur after control of hyperthyroidism with thiourea. Patient B36869 who had been on 210 mg. of thiourea and 15 drops of strong solution of iodine daily had an iodine of 11 gamma in spite of the fact that his basal metabolic rate was +8% and his pulse 66. Not too much significance can be attached to the iodines above 8 gamma of 4 other patients in whom hyperthyroidism seemed to be controlled. All of them were taking only 50 mg. of thiourea and 15 drops of strong solution of iodine daily. One had had serum precipitable iodines in the euthyroid range when on larger doses of thiourea. Two did not follow precisely the prescribed medication. The fourth had improved clinically without reduction in basal metabolic rate. Of the 36 patients with serum precipitable iodines above 8 gamma, 23 were those patients whose hyperthyroidism had been only partially controlled by thiourea. Six had iodines ranging from 8 to 8.4 gamma, values which

differ from the euthyroid maximum by less than the experimental error of the method. Two had stopped thiourea 1 and 2 months previously. As yet it is too soon to know if the increase in serum precipitable iodine represents an exacerbation of hyperthyroid symptoms, or a temporary rebound after withdrawal of thiourea.

Clinical improvement in symptoms and signs, such as nervousness, palpitation, vasomotor phenomena and tremor accompanied the gain in body weight, the disappearance of tachycardia, and the return to normal of the rate of oxygen consumption and the level of hormonal iodine.

It is of interest in view of the frequent increases in exophthalmos reported after thyroidectomy¹³ that in no instance was there any discernible progression in eye signs. Furthermore, in 5 of these patients with pronounced and unequal exophthalmos distinct subjective and objective improvement occurred. In 1 of these, serial observations were made by an ophthalmologist which revealed regression toward normal concomitantly with treatment by thiourea and strong solution of iodine.³

Congestive failure decreased or disappeared in all 12 patients in whom objective findings were present prior to treatment. Control of the hyperthyroidism undoubtedly played a rôle in this improvement but this cannot be proven because digitalis was given as well. Fibrillation persisted, however, in all but 1 of the patients.

In this series of patients no definite toxic reactions were observed. Occasional patients reported anorexia and nausea at the start of therapy. This invariably disappeared, however, following continued therapy with the same, or with smaller doses of thiourea. In 3 subjects, aged 72, 70 and 44 respectively, ulcerations appeared following thrombophlebitis of varicosities of the lower legs. Since these healed in the face of continued medication, classification of these developments as toxic manifestations seems unwarranted. No untoward changes in the formed elements of the blood and urinalyses were

noted during treatment of 118 patients in this group. In a previous report 2 patients who developed drug fever shortly after beginning thiourea have been noted.² These are not included in this report, since treatment lasted but a few days.

Effects of Thiourea Withdrawal. Data are available on 8 patients who have been observed for 5 to 16 months following a course of thiourea which lasted from 6.2 to 24 months. The current status of these patients together with data from the antecedent history is presented in Table 2. At the time the thiourea was stopped the body weight had increased in all but 1 patient, Pe, who voluntarily restricted her caloric intake. The highest pulse rate after treatment was 80, and the basal metabolic rates ranged from -29 to +8%. The serum precipitable iodine was less than 8 gamma per 100 cc. in all members of this group.

Despite withdrawal of thiourea body weight changes, the pulse rate and the

basal metabolic rate are still within euthyroid limits in all 8 patients. The serum precipitable iodines, however, have again risen above 8 gamma in 3 of the 8 subjects in whom it has been measured. To date this last change has been accompanied by recurrence of clinical symptoms of hyperthyroidism in 1 of these patients, So, while the other 2 patients have failed to return for their appointments.

Discussion. These results with unselected patients indicate that long-term medical treatment of hyperthyroidism is quite practical in most cases. Within 1 to 2 months of the start of thiourea therapy, preferably supplemented by the administration of strong solution of iodine, the patient reports subjective improvement. This is accompanied by objective evidences of a decreased level of metabolism with a cancellation of body weight losses and a disappearance of the tachycardia. This favorable clinical response is elicited, however, only when an optimal therapeutic

TABLE 2.—STATUS OF PATIENTS 5 TO 16 MONTHS FOLLOWING WITHDRAWAL OF THIOUREA

Patient	Time from start (mos.)	Thiourea (mg. per day)	Strong solution iodine (drops per day)	Body weight (kg.)	Pulse rate (per min.)	BMR (%)	Serum precipitable iodine (gamma per 100 cc.)
B59207	0	56.5	104	+11	10.9
	0-20	280-25	XV	57.8	74	+6	5.6
	20-32	0	0	71.0	88	-5	5.3
B58332	0	53.0	84	+37	10.6
	0-22	280-25	0	55.0	60	..	5.6
	22-28.5	0	0	57.4	72	..	5.8
50359	0	49.9	84	+41	9.8
	0-18	280-25	XV	61.4	70	-14	2.6
	18-28	0	XV	63.5	84	+19	13.4
A34630	0	63.8	100	+31	8.2
	0-23	280-15	0	66.0	66	+1	7.3
	23-28	0	0	65.0	66	-8	5.4
Pe	0	51.1	68	+23	11.3
	0-17	70	XV	48.1	80	-5	7.6
	17-33	0	XV	+12	..
B70975	0	60.3	80	+54	11.6
	0-7.2	210	0	66.1	56	+8	5.6
	7.8-19.7	0	0	64.7	76	+6	4.5
So	0	65.0	98	+36	11.1
	0-6.2	210-35	XV	70.0	64	-28	3.2
	6.2-17.2	0	XV	67.9	78	+16	12.3
A10703	0	59.2	84	+31	12.0
	0-24	280-25	0	80.3	60	-15	5.5
	24-32.2	0	0	82.9	56	-17	8.3

tic regimen is employed. This must include the administration of thiourea in effective doses. For most patients this has been found to be 75 to 210 mg. daily.¹⁶ The clinical response to these amounts of thiourea is enhanced by the concomitant use of strong solution of iodine. Not only does it accelerate the onset of the remission, but it also increases the magnitude of the response.² This is true even though iodine solution has been given prior to the start of thiourea. This action of iodine continues during prolonged treatment, since its withdrawal often produces an exacerbation in previously controlled hyperthyroidism, despite a continued intake of thiourea.² These additive effects of thiourea and iodine solution have been amply demonstrated in control studies and may be attributed to the capacity of iodine solution to act directly on the thyroid gland, inducing a resting phase and at the same time blocking thyrotropic hormone which increases thyroid activity.¹⁰ These 2 actions tend to decrease thyroid oversecretion and do not inhibit thiourea and related compounds from blocking the conversion of diiodotyrosine and thyroxine to thyroid hormone. The impression, held at first, that iodine interfered, was based in part on sporadic cases which would have responded poorly under any circumstances, and in part on clinical experiences in which the iodine solution was discontinued at the time the antithyroid drug was started.²

The ideal therapeutic program should also include adjustments in the dose of thiourea once the hyperthyroidism has been brought under control. Otherwise the continued administration of the drug in the amounts initially used to induce a remission may result in hypothyroidism or myxedema. This can be prevented or corrected by reducing the intake to as low as 50 or 25 mg. daily or by adding desiccated thyroid, 0.03 gm. or more, to the therapeutic regimen.^{2,16} The first adjustment is to be preferred, since it minimizes the number of medications and

the amount of thiourea taken by the patient.

The importance of an optimal therapeutic regimen is emphasized by the results in this group of patients. Failure of the basal metabolic rate to decrease to normal in approximately one-fifth of the patients, for example, is to be ascribed to an inadequate therapeutic regimen in all but 1 instance. Thus 7 of the patients were started on an intake of 15 to 50 and 2 others on 75 mg. of thiourea daily, amounts which, it is now known, frequently prove inadequate. In 3 patients the maintenance dose was reduced to 15 mg. which has since been shown to be insufficient. In the 1 patient who received an adequate intake of thiourea, 210 mg. daily, strong solution of iodine was withheld. There is no reason to assume that with therapy closer to optimum these patients would not have responded satisfactorily. This point of view is supported by the observation that despite inadequate therapy the basal metabolic rate declined toward normal in most of these patients. In the group in which a partial return of the basal metabolic rate occurred the average value before treatment was +50%, and +29% after therapy. The presence of a certain number of such cases with an incomplete or absent response is apparent in retrospect, since in the experimental plan designed to elucidate certain principles of treatment patients were placed on regimen which now appear to be not entirely adequate. It is quite likely that strict adherence to the therapeutic principles which have since been established would have yielded more satisfactory results.

Other factors may, however, be operative as well in preventing an adequate clinical response. In the group which continued to lose weight, persistent thyroid overactivity was evident in only one-half of the patients. In these treatment was unsuccessful either because the prescribed regimen was inadequate or, less often, because the patient failed to follow instruction. In the remainder the weight

loss resulted from other causes. Ulcerative colitis was present, for example, in 1 patient, 3 patients lost weight following normal pregnancies and deliveries, and 3 voluntarily restricted their intake of food. This interpretation is supported by the associated findings of a decrease in clinical symptoms and signs as well as in the basal metabolic and pulse rates.

The finding of precipitable iodine values greater than 8 gamma per 100 cc. in patients several months after they have been taken off thiourea suggests that some measure of thyroid overactivity still exists. In 1 patient adequately followed this was associated with clinical evidences of a recurrence of hyperthyroidism. The significance of the rise in serum precipitable iodine of 2 other patients without simultaneous definite signs of hypermetabolism is as yet undetermined. Several possibilities exist. The original disease may still be present in an attenuated form detectable only by a sensitive test such as the serum precipitable iodine. On the other hand the dissociation may merely be a lag phenomenon, and with time clinical and other laboratory evidence of increased metabolism may appear in these patients. The question as to the probability of an ultimate cure of hyperthyroidism by prolonged medical treatment remains unsettled.

That the measurement of serum precipitable iodine is an extremely sensitive test of hyperthyroidism is exemplified in a detailed study of the patients. The patients in Table 1 after treatment frequently responded poorly with respect to only 1 of the 3 criteria, weight change, pulse rate or basal metabolic rate, yet in addition the serum precipitable iodine remained above 8 gamma per 100 cc. That is why the percentage of cases with iodines above 8 gamma is approximately equal to the sum of the percentages of cases without satisfactory weight gain, reduction in pulse rate and decrease in basal metabolic rate.

Omission of iodine solution in prolonged treatment may increase the possibility of a permanent remission or cure. Since

only 13 of the 89 patients were not given iodine solution, no conclusion can be drawn. However, of the 8 patients listed in Table 2 whose hyperthyroid symptoms had abated sufficiently to permit withdrawal of thiourea medication, 5 had not been given iodine solution. The patient, So, in whom hyperthyroid symptoms recurred to a degree that she returned to thiourea medication, was 1 of the patients who had been treated previously with both strong solution of iodine and thiourea.

There are advantages and disadvantages inherent in any type of treatment for hyperthyroidism, whether it be medication with antithyroid compounds, surgical removal of the gland, or irradiation of the gland directly or by the administration of radioactive iodine. The problems of the individual patient may be of considerable help in making this decision. A medical regimen is undoubtedly the treatment of choice for elderly patients, for those with heart disease, with exophthalmos or with hyperthyroidism recurring after thyroidectomy. Possibility of anesthetic or operative death, recurrent laryngeal nerve injury, progression of exophthalmos or hyperparathyroid tetany are all eliminated. Statistics indicate that these risks are by no means inconsiderable. The mortality associated with thyroid surgery, for example, ranges up to 3%⁵ and is undoubtedly higher in smaller clinics. Injuries to the nerve supply of the vocal cords are by no means rare. Exophthalmos is reported to progress following thyroidectomy in more than one-half of the patients with toxic diffuse goiters.¹³ Hypoparathyroid tetany is a definite risk in patients subjected to thyroid ablation. Moreover, both recurrence of hyperthyroidism (13 to 25% of cases) and postoperative myxedema are not infrequent sequelae of thyroidectomy.^{6,9,17} Radioactive iodine therapy of hyperthyroidism will, of course, obviate most of the risks inherent in surgical treatment of hyperthyroidism. It may well create new problems. The questions as to whether the course of renal disease will

be accelerated by passage of the radioactive isotope through the glomeruli and tubules, and whether irradiation of the thyroid gland will predispose to neoplasia are as yet unanswered.

Disadvantages often cited in criticism of medical control of hypothyroidism apply also to other methods of treating thyroid overactivity. The patient's co-operation is necessary and interval visits for check-ups over long periods of time must be continued, whether medical treatment or surgical intervention has been selected. If either treatment is improperly conducted, myxedema or exacerbations will develop. Medical treatment does fail to relieve pressure symptoms and deformities. Also, it is not entirely benign. Reactions to thiourea in our own series have been limited to occasional gastro-intestinal distress and to drug fever in 2 patients. With much larger amounts of this drug, since shown to be unnecessary, other untoward effects have been

reported.^{8,12} On the whole, however, thiourea has proven to be less toxic than thiouracil.^{4,14} Other compounds such as propyl-thiouracil may, however, prove to be as efficacious and non-toxic as thiourea. The principles established for the use of thiourea should be applicable to other goitrogenic substances, since they are based on the fundamental physiology of the thyroid.

Summary and Conclusions. 1. One hundred and eighteen patients with hyperthyroidism have been treated with thiourea, usually supplemented by strong solution of iodine. Of these, 89 were followed for periods of 6 months to more than 2 years.

2. Thyroid overactivity can be controlled for long periods by these means with a minimal incidence of toxic reactions. In a small proportion of patients the hyperthyroidism seems to have disappeared.

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RUTIN THERAPY FOR INCREASED CAPILLARY FRAGILITY AND RETINOPATHY ASSOCIATED WITH DIABETES MELLITUS*

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RUTIN has recently been introduced into the physicians' armamentarium for the treatment of hemorrhagic states manifested by increased capillary fragility. Rutin, as used today, is a flavonal glucoside isolated from the early blossoming leaves of the buckwheat plant.⁵ It was originally discovered in buckwheat in 1860 and has also been obtained from tobacco leaf and rice herbs.

Several clinical reports have appeared concerning successful therapeutic results when the drug is used in daily doses of 60 to 180 mg. and no toxic effects have been reported with the purified drug regardless of the dosage. Griffith and his co-workers^{15,16,17} found an increased capillary fragility among hypertensive patients by means of the positive pressure test of Göthlin. They reported that with rutin therapy the fragility became normal in 75% of these patients. Shanno⁴¹ has found rutin to be of definite value in preventing the increased capillary fragility associated with thiocyanate therapy for hypertension. Kushlan²¹ has reported the successful use of rutin in arresting hemorrhage in a case of hereditary telangiectasia and Lindauer²⁸ in cases of idiopathic pulmonary hemorrhage. Good results in the treatment of increased capillary fragility in hypertensive patients was also reported by Zfass⁴⁹ who found that larger doses were needed

in some patients in order to obtain the desired results. Recently, however, McManus and Landrigan³⁰ claimed to have found no effect of rutin on the increased capillary fragility of 10 patients after 1 month of therapy.

It should be pointed out that most of these studies with rutin have observed its effects on increased capillary fragility in relatively few diseases. Since decreased resistance of capillaries is not confined to a single disease, a brief discussion of the various factors involved in capillary fragility may be considered.

THE GENERAL PROBLEM OF CAPILLARY FRAGILITY. There are many observations concerning the association of increased capillary fragility with various diseases unrelated to thrombocytopenia; these date back many years to Rumpel's³⁹ observations of increased capillary fragility in scarlet fever in 1909, and Leede's²⁶ confirmation 2 years later. It has been observed in scurvy,^{1,2,5,12,13,19,20,32,48} allergy in children,³⁷ numerous skin diseases,^{11,31} tuberculosis in children,¹⁰ various toxic and poison states,⁴⁵ hypertension,^{15,16,17,41} rheumatic fever,²² diabetes mellitus,^{3,29,38} rheumatoid arthritis,⁴⁴ and newborn infants.²¹

It is not surprising, then, to learn that different *pathologic* mechanisms are found in different cases with increased capillary fragility. In a recent review, Peck and

* The rutin used in this investigation was supplied by the Upjohn and Maltine Companies.

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Copley³⁴ have classified these as due to: (a) rupture of a blood-vessel, (b) perforation of a blood vessel (corrosive or ulcerative), and (c) diapedesis through the unruptured, non-perforated wall of a blood-vessel. There is also evidence that various types of *physiologic* alterations may be the bases for these different pathologic causes. Increased hyaluronidase activity may liquefy pericapillary supporting tissue which is known to contain hyaluronic acid. Damage to endothelial tissue may prevent this tissue from secreting an interendothelial cement substance which has been found to act as a protective coating for the endothelium facing the lumen. Finally, changes in the elastic tissue around the capillaries may eliminate a cushioning effect that such elastic tissues are known to have and thus facilitate rupture when pressure is applied. Because of the several mechanisms responsible for increased capillary fragility, Peck warns that "the finding that capillary fragility is counteracted by any one treatment must be qualified by the specific conditions under which the subject happens to be during such treatment." Also a successful treatment for capillary fragility occurring in one disease state may have no effect in another disease.

Numerous tests to determine the state of the capillaries have been devised. The tests which have been most popularly used are: (a) *negative pressure tests* devised by Hecht¹⁸ and subsequently modified by numerous investigators;^{6,7,42} (b) *positive pressure tests* based on the Rumpel-Leede^{26,39} test and modified by Göthlin^{12,13} and Wright and Lilienfeld;⁴⁸ (c) *puncture tests*;²³ (d) Flicking test;²¹ (e) *Snake venom test*;^{35,56} and (f) *concentrated saline test*.²⁷ Wright⁴⁷ suggests that the results of any test must not be over-interpreted and that a positive test gives no indication as to the etiology of the increased fragility. To complicate the general problem, the various tests, particularly the negative and positive pressure tests, do not necessarily correlate,⁴ and so care must be observed in comparing the results of different investigators.

Furthermore, it should be noted that results of positive pressure tests may vary in the 2 arms of the same individual at the same time.¹⁴

RETINOPATHY AND CAPILLARY FRAGILITY IN DIABETES MELLITUS. Using various tests, many workers have found a greater incidence of increased capillary fragility in diabetics than in non-diabetics. Using a positive pressure test, Beaser and his co-workers³ found a decreased capillary resistance in 100% of their diabetic patients with associated hypertension and in 54% without hypertension; the incidence was greatest in the 5th and 6th decades. Mallery,²⁹ using positive and negative pressure tests, found abnormal capillary fragility in 30 of 120 patients with the disease. Other factors, such as vitamin C deficiency, prothrombin deficiency and thrombocytopenia, were ruled out as causes. Joslin²² reports studies performed on 100 patients in his clinic with the Göthlin technique; increased capillary fragility was found in 41. Using capillary microscopy, Davis⁸ found 4 cases of spontaneous capillary petechiae among 26 diabetics.

A close association has been reported between the increased skin capillary fragility found by various tests in diabetic patients and diabetic retinopathy. Thus, Mallery²⁹ found that in the 30 diabetic patients with positive skin tests, 24 also had retinitis. In a series of 38 patients with diabetic retinitis the same author found 63% to have low capillary resistance. Of the 41 above-mentioned cases found by Joslin²² to have increased Göthlin indices, 26 had retinitis, 12 were hypertensives without retinitis and only 3 were without hypertension or retinitis. Wagener⁴³ reports the studies of Foxworthy at the Mayo Clinic using a positive pressure method in patients without arterial hypertension. In a group of 85 non-diabetic patients of varying ages, the appearance time of the first petechia was 4.9 minutes, and after 10 minutes the average number of petechiae in a circle the size of a quarter was 14. Among

69 patients suffering from diabetes, without retinopathy, the appearance time was 2.36 minutes and the number of petechiae was 41. Among 44 diabetics with retinopathy the average petechial appearance time was 1.5 minutes and their average number was 101. In only 1 of the patients with retinitis was there a normal petechial appearance time and in 4 was the petechial count less than 25.

Rudy and his co-workers³⁸ studied 6 patients with increased capillary fragility and associated diabetic retinitis. None of these responded to hesperidin (vitamin P) therapy. Foxworthy is reported by Wagener³³ to have noticed no improvement in the retinopathy of her patients treated with hesperidin, although she noted that the skin capillary fragility improved in many.

Method of Study. In this study an attempt was made to determine the effects of rutin on the capillary fragility and retinopathy of diabetic patients and to ascertain whether any improvement in one was accompanied by changes in the other. Twelve diabetic patients with diabetic retinal hemorrhages and with markedly increased capillary fragility were studied. The former complication had been discovered and charted by the members of the eye staff of the hospital. The patients were saturated with ascorbic acid, 100 mg. t.i.d., for 1 month prior to treatment. They were then given rutin, 20 mg. t.i.d., daily for 2 months; the dose was increased to 40 mg. t.i.d. for another month. Five patients were given ascorbic acid, 100 mg., 3 times daily, with the rutin during the entire period of study.

Capillary permeability was studied by the fluorescein method of Lange²⁵ in 9 of the patients. All 9 tested had normal capillary permeability as determined by this method before treatment was instituted. For this reason additional fluorescein studies were discontinued.

Capillary fragility was determined by the positive pressure test as modified by Wright and Lilienfeld.⁴ The blood pressure cuff was applied to the upper arm for 15 minutes at a pressure midway between systolic and diastolic pressures. Two to 4 minutes after the cuff was released, the number of petechiae were counted in a 2.5 cm. circle on the flexor

surface of the forearm 4 cm. below the crease of the elbow.

During the 3 months of the study, the patients were maintained on adequate diets. All except 1 received insulin, the range of the dosage varying from 10 to 55 units. Only 2 of the patients had glycosuria during the period of observation. None reported insulin hypoglycemic reactions. Throughout the period of observation no changes were made in the diabetic regimen of any patient so that improvement could not be due to better diabetic management.

Each patient had been followed in the ophthalmology clinic. One of the authors (M. R. C.) reexamined and charted the ophthalmoscopic findings at each visit to insure a close check-up for any retinal changes. A disappearance of any of the previously charted retinal hemorrhages, without the advent of new areas, was recorded as an improvement.

The results of the study are summarized in Table 1. The age and blood pressure are also recorded since these are important factors in studies concerning capillary resistance.

Results and Comments. After treatment marked improvement in skin capillary fragility occurred in only 3 of the 12 patients, and slight improvement in 1. Two of these 4 had hypertension in whom the blood pressure dropped to normal levels while under observation; the other 2 had normal blood pressure.

Punctate hemorrhages of the type associated with diabetes were found in 23 fundi of the 12 patients at the onset of the study. After rutin therapy for 3 months, improvement was found in only 5 of these eye-grounds. Two of the patients in whom retinal improvement occurred did not demonstrate an improvement in the skin capillary fragility. Two patients who showed an increase in skin capillary resistance did not demonstrate any improvement in the ophthalmoscopic picture. There were only 2 patients in this series who showed improvement in both the retinal picture and skin capillary fragility. Both of these had hypertension whose blood pressure returned to normal while under observation.

TABLE 1.—RESULTS OF CAPILLARY FRAGILITY TESTS AND OPHTHALMOSCOPIC EXAMINATION OF 12 DIABETICS BEFORE AND AFTER RUTIN THERAPY FOR 3 MONTHS

Patient	Age (yr.)	Sex	Duration of diabetes (yr.)	Associated diseases	Before treatment				After 2 months therapy (60 mg., q.d.)				After 3 months therapy (120 mg., q.d.)			
					Blood pressure	Capillary fragility	Retinitis		Blood pressure	Capillary fragility			Blood pressure	Capillary fragility	Retinitis	
218441	65	M	4	Psoriasis; old hemiplegia	116/70	4+	+	+	120/70	Normal			110/70	Normal	+	+
8389	67	F	26	Osteoarthritis	140/80	4+	+	+	140/80	4+			170/90	4+	+	Imp.
175493	54	F	8	"	130/80	4+	+	+	150/80	4+			116/64	4+	+	+
151025	68	F	11	"	180/90	4+	+	+	150/80	4+			140/80	4+	+	+
1410	52	F	3	Uterine bleeding	150/90	4+	+	+	118/70	4+			130/70	4+	+	+
10201	41	M	1	Prostate hypertrophy	90/68	4+	+	+	120/80	4+			120/80	4+	+	+
97394	51	F	14	"	160/80	4+	+	+	140/70	4+			160/80	4+	+	+
188967	70	M	16	"	168/80	4+	+	+	160/80	2+			130/60	1+	Imp.	+
212723	50	F	11	Hypertensive cardiac	194/106	4+	+	+	140/90	2+			140/80	1+	Imp.	+
201410	54	M	4	Healed tuberculosis	160/90	4+	0	+	140/100	4+			130/90	4+	0	Imp.
118655	51	F	?	"	108/74	4+	+	+	110/80	4+			110/80	4+	+	+
221731	47	M	23	Neuropathy	135/90	4+	+	+	130/80	3+			130/80	3+	Worse	Worse

Capillary fragility (Wright and Lilienfeld technique): recorded as follows: 0 to 10 petechiae normal; 10 to 20 petechiae labelled 1+; 20 to 50 labelled 2+; 50 to 100 labelled 3+; 100 to 400 designated 4+. Retinal hemorrhage present is designated by +; none present designated by 0; improvement designated by Imp.; progression of retinitis designated Worse.

None of the improvement could be attributed to better diabetic control; nor could it be correlated with the blood glucose level, the blood cholesterol, serum albumen and globulin levels or concomitant ascorbic acid therapy. Concerning the improvement found in the retinal picture presented by these patients the small number showing resorption of the hemorrhages is within the amount that can be found without rutin therapy when good control of the diabetes is maintained in a patient. It must be pointed out that whereas increased capillary fragility may play a great rôle, factors such as severe exertion²⁹ or insulin hypoglycæmic reaction⁴⁶ can precipitate retinal hemorrhages in diabetic patients. Factors of this type may be the cause of retinal hemorrhages which disappear after a time, only to reappear. Dolger⁹ followed 200 younger diabetic patients up to 25 years and concluded that not one escaped retinopathy, albuminuria and/or hypertension. He found that retinal hemorrhage was the predominant vascular lesion and often preceded the appearance of albumen or hypertension. These retinal lesions were not always permanent or progressive. A recent study of patients with diabetic retinitis by Schneider *et al.*⁴⁰ found marked improvement in retinal hemorrhages of their patients treated with high protein diets.

With all the variable factors that might lead to improvement of diabetic retinitis, it is difficult to ascribe our results to rutin

therapy. One of our patients (the twelfth in Table 1) who showed some decrease in skin capillary fragility after therapy, showed a rapid resorption of the hemorrhages in the fundus after 1 month; these areas were quickly replaced by large exudates and within a short period retinitis proliferans developed. During the period on rutin therapy, he had undergone a tremendous amount of emotional stress; his blood pressure and diabetic control had remained excellent. This patient not only illustrated that rapid progression of retinitis could take place while under rutin therapy, but also demonstrated the difficulty of establishing an etiologic agent.

Conclusions. 1. Twelve diabetic patients with both increased skin capillary fragility and retinal hemorrhages were treated with rutin for 3 months.

2. Marked improvement in skin capillary fragility was found in 3 and moderate improvement in 1. In 2 of these the changes accompanied a reduction of hypertension.

3. Only 5 fundi (4 patients) of 23 improved; in 2 of the 5, the retinal hemorrhages cleared up completely. This improvement cannot be directly attributed to rutin. Diabetic retinitis progressed rapidly in 1 patient while under treatment.

4. In 2 patients, the retinal lesions improved without a change in the increased skin capillary fragility and in a similar number, the skin capillary resistance increased without retinal improvement.

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THE SYNERGISTIC OR ADDITIVE ACTIVITY OF CHEMOTHERAPEUTIC COMPOUNDS*

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In chemotherapy the matter of administration of 2 compounds conjointly in the treatment of some of the infectious diseases is of considerable clinical interest and importance. This is based upon the fact that better therapeutic results may be expected or observed than from the administration of either compound alone. Since such combined therapy usually permits the administration of smaller doses of each compound than ordinarily required of either alone, the possibility of preventing or reducing toxic effects and reactions is readily apparent, aside from the fact that it sometimes offers a means for the successful treatment of mixed infections. Furthermore, it appears that such combined chemotherapy may prevent or reduce the chances of so-called acquired drug resistance of infecting microorganisms and especially in relation to the sulfonamide and antibiotic compounds.

MECHANISM OF SYNERGISTIC OR ADDITIVE ACTIVITY. Theoretically there would appear to be at least 3 possible explanations for the enhanced curative effects of combined chemotherapy. In the first place, 1 compound may aid, cooperate with or potentiate the other with a material increase of antimicrobial effects designated as synergistic activity. Indeed, this potentiating or true synergistic activity may not require the presence of a second chemotherapeutic compound at all, since Frieden¹³ has observed that the vitamin nicotinamide apparently has this effect upon penicillin *in vitro* for *Staph. aureus* while Schwartzman¹⁷ states that the sus-

ceptibility of highly resistant gram-negative bacilli to penicillin *in vitro* may be greatly increased by the addition of such amino acids as methione, threonine and methionine sulfoxide, methione being essential for the synergistic effects.

On the other hand, however, the enhanced therapeutic activity may be merely a summation of the antimicrobial effects of the 2 compounds acting independently of each other, designated as additive activity; or thirdly, as suggested by Klein and Kalter,²² the effects may be due to the fact that 1 compound, like penicillin, sharply reduces the total number of microorganisms which permits another, like a sulfonamide compound, which is only partially bacteriostatic or bactericidal in the presence of a large number of cells, to become more active in the presence of a smaller number of cells.

Be this as it may, however, it is quite certain that synergistic or additive chemotherapeutic activity is not to be expected either *in vitro* or *in vivo* unless the microorganism is susceptible to both of the compounds being employed, although it may be much more susceptible to one than to the other. Furthermore, it is to be expected that the results observed by different investigators working with the same compounds and the same microorganism will vary according to the susceptibility of the particular strain of culture employed and to other technical factors as well. But since it is difficult and sometimes impossible to distinguish between true synergistic and mere additive activ-

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ity, I have preferred to designate the results of my investigation herewith summarized as synergistic or additive, since these are not strictly synonymous terms.

SYNERGISTIC OR ADDITIVE ACTIVITY OF COMPOUNDS IN VITRO. In 1943 Ungar⁴⁵ reported that sulfapyridine and sulfathiazole almost doubled the activity of penicillin against cultures of *Staph. aureus* and hemolytic streptococcus *in vitro*, although the effects varied according to the resistance of the strains employed. Similar results were also observed by Bigger² who reported that sulfanilamide, sulfathiazole and sulfapyridine greatly increased the activity of penicillin against these microorganisms; this investigator has also reported that penicillin and sulfathiazole together had a pronounced effect upon the typhoid bacillus.³

T'ung⁴¹ has reported that 8 out of 15 strains of brucella were somewhat susceptible to penicillin and that the addition of small amounts of sulfathiazole increased the antimicrobial effects. Kirby²¹ has also observed that sulfonamide-penicillin and urea-penicillin mixtures produced greater bacteriostasis than penicillin alone, which appeared to be additive rather than truly synergistic. Chain and Duthie⁷ state that sulfanilamide and sulfamezathine have no antagonistic action on the bactericidal effects of penicillin on staphylococci and streptococci but, on the contrary, possess synergistic activity and especially on staphylococci having a natural resistance to penicillin. Similar results have been reported by Klein and Kalter²² with the sulfonamide-resistant and sulfonamide-susceptible strains of *Staph. aureus* in mixtures of penicillin with sulfathiazole, sulfadiazine or sulfapyridine. Massell and his associates³³ have reported that while the minimal effective concentrations of penicillin for many strains of streptococci of the viridans type were increased *in vitro* by the sulfonamide compounds, no enhancement of activity of penicillin was observed, however, in the presence of amounts of the compound above its minimal effective concentrations. In this con-

nection it is also to be stated that Himmelweit¹⁷ observed that penicillin is not only without effect upon staphylococcus bacteriophage but that these chemotherapeutic agents act together synergistically with more rapid killing of the organisms than either alone.

Hobby and Dawson,¹⁸ however, have not observed a synergistic action between sulfadiazine or sulfapyridine and penicillin *in vitro* for *Staph. aureus* and hemolytic streptococcus; on the contrary, sulfadiazine appeared to decrease the rate of action of penicillin although, in a later study, they observed a synergistic or additive effect of sulfadiazine against organisms sensitive to this compound with more pronounced effects in the mixtures of penicillin and sulfadiazine than with either compound alone.¹⁹ On the other hand, Garrod¹⁴ has stated that sulfathiazole reduces the velocity of the action of penicillin on staphylococci *in vitro* by about one-half, and Cohn and Seijo⁸ have also reported that the growths of sulfonamide-resistant strains of gonococci were not affected by combinations of "subtherapeutic" amounts of penicillin and sulfathiazole.

Insofar as results *in vitro* are concerned, therefore, it would appear that the sulfonamide compounds may or may not increase the antibacterial effects of penicillin, although the majority of investigators have observed synergistic or additive activity. In this connection, however, the possible synergistic or additive effects of penicillin and streptomycin *in vitro* are of additional interest and importance. In my laboratory Bondi and Dietz have observed that the smallest amount of penicillin giving complete inhibition of the H strain of *Staph. aureus* in a serial dilution method was 0.2 unit, while the minimal inhibitory amount of streptomycin was 0.001 mg. (1 unit). In mixtures of the 2 compounds, however, the minimal inhibitory amount of penicillin was 0.05 unit of penicillin and 0.0005 mg. (0.5 unit) of streptomycin, indicative of a slight degree of synergistic

or additive activity. With the SM strain of *Staph. aureus* the minimal inhibitory amounts of penicillin was 0.1 unit and 0.001 mg. (1 unit) of streptomycin, while in mixtures of the 2 compounds, the minimal inhibitory amount of penicillin was 0.05 unit and 0.0005 mg. (0.5 unit) of streptomycin and, therefore, likewise indicative of some degree of synergistic or additive activity.

Of further interest in this connection are the observations of Carpenter and his colleagues⁶ who found that while gonococci readily acquired resistance to sodium sulfathiazole, rivanol lactate and promin *in vitro*, yet when the organisms were exposed to mixtures of these 3 compounds much less resistance was acquired, while exposure to the mixtures, plus penicillin, resulted in no acquisition of resistance at all. But since it appears as well established that so-called acquired resistance of microbial agents is due to the survival of variants naturally resistant to a given concentration of a compound, any second compound that in itself inhibits the rapid multiplication of such variants or destroys them may prevent so-called acquired resistance or reduce the rate at which it develops. Whether or not similar effects occur *in vivo* in the treatment of experimental and human infections has not been determined, but since this is both possible and probable in synergistic or additive chemotherapy, the matter is of great clinical interest and practical importance.

SYNERGISTIC OR ADDITIVE ACTIVITY OF COMPOUNDS IN THE TREATMENT OF EXPERIMENTAL INFECTIONS. Much less attention has been given to synergistic or additive chemotherapy in the treatment of experimental infections of the lower animals. And yet such investigations would appear to be of more importance in relation to clinical medicine than studies *in vitro* in spite of the limitations and caution required in interpreting the results observed in the treatment of the acute and chronic infectious diseases of human beings.

Soo-Hoo and Schnitzer¹⁰ have reported that penicillin and sulfapyridine, as well as penicillin and sulfanilamide, in subtherapeutic doses, had a pronounced synergistic activity in the treatment of experimental streptococcal infections, while Sultan, Jenkins and Cutting¹¹ state that in pneumococcal and streptococcal infections in mice slightly more favorable results were observed by simultaneous treatment with penicillin and sulfadiazine than to treatment with either compound alone. Eagle, Magnuson and Fleischman¹² have also found that penicillin and mapharsen (oxophenarsine hydrochloride) are synergistic in the treatment of experimental syphilis of rabbits.

Smith and McCloskey¹³ have reported that while promin and other sulfone compounds alone were relatively ineffective in the treatment of experimental tuberculosis, combined treatment with these compounds and streptomycin gave better results than streptomycin alone, since they were greater than the sum of effects from the individual compounds. Callomon, Kolmer, Rule and Paul⁵ have also observed that while diasone and especially streptomycin alone exerted a suppressive effects in the treatment of experimental tuberculosis of guinea pigs, particularly noteworthy therapeutic effects were observed following combined streptomycin and diasone therapy which were likewise highly suggestive of a synergistic or additive chemotherapeutic activity. In this connection it also may be stated that while Hodges²⁰ observed penicillin to be ineffective and streptomycin but slightly effective in the treatment of developing chick embryos infected with feces, combined penicillin and streptomycin therapy was highly effective.

It appears, therefore, that the results of these investigations on the combined chemotherapy of various experimental infections of the lower animals have clearly indicated synergistic or additive effects. This is certainly true of the various experimental infections treated by me with various combinations of chemotherapeutic

compounds, the results of which may be briefly summarized herewith with the important details shown in the accompanying tables.

Thus, as shown in Table 1, it appears that while both penicillin by intermittent intraabdominal injection and sulfathiazole by ingestion were effective in the treatment of mice (approximately 20 gm. each) inoculated intravenously with 0.05 cc. of a 24 hour broth culture of a virulent strain of *Staph. aureus*, susceptible to both compounds *in vitro*, synergistic or additive effects were observed following the administration of both compounds at the

same time. Thus of 20 mice given penicillin in total doses of 240 units per animal, by intermittent intraabdominal injection, 6 (30%) survived, while of 20 given total doses of 12 mg. of sulfathiazole per animal by ingestion, 4 (20%) survived; whereas of 20 given both compounds in these total dosages 16 (80%) survived with 45% survivals among those given 120 units of penicillin with 12 mg. of sulfathiazole and 25% survivals among those given 60 units of penicillin and 12 mg. of sulfathiazole.

Similar synergistic or additive effects were observed in mice inoculated intra-

TABLE 1.—SYNERGISTIC OR ADDITIVE ACTIVITY OF PENICILLIN AND SULFATHIAZOLE IN THE TREATMENT OF EXPERIMENTAL STAPHYLOCOCCUS AUREUS INFECTIONS OF MICE*

No.	Penicillin†		Sulfathiazole‡		Survivals§	
	Dose (units per mouse)	Total dosage (units per mouse)	Dose (mg. per mouse)	Total dosage (mg. per mouse)	No.	%
20	60	720	20	100
20	30	360	16	80
20	20	240	6	30
20	10	120	0	0
20	5	60	0	0
20	2 0	24 0	11	55
20	1 0	12 0	4	20
20	20	240	1 0	12 0	16	80
20	10	120	1 0	12 0	9	45
20	5	60	1 0	12 0	5	25
30	Controls	4	13 3

* Inoculated intravenously with 0.05 cc. of 24 hour broth culture.

† Administered intraabdominally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 12 doses.

‡ Administered orally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 12 doses.

§ Eight days after inoculation.

TABLE 2.—SYNERGISTIC OR ADDITIVE ACTIVITY OF PENICILLIN AND SULFADIAZINE IN THE TREATMENT OF HEMOLYTIC STREPTOCOCCUS (GROUP A) INFECTIONS OF MICE*

No.	Penicillin†		Sulfadiazine‡		Survival§	
	Dose (units per mouse)	Total dosage (units per mouse)	Dose (mg. per mouse)	Total dosage (mg. per mouse)	No.	%
20	30	360	.	.	18	90
20	20	240	.	.	14	70
20	10	120	.	.	6	30
20	5	60	.	.	0	0
20	2 0	24 0	6	30
20	1 0	12 0	2	10
20	20	240	1 0	12 0	20	100
20	10	120	1 0	12 0	14	70
20	5	60	1 0	12 0	6	30
40	Controls	0	0

* Inoculated intraabdominally with approximately 10,000 M.L.D. of culture.

† Administered intraabdominally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 12 doses.

‡ Administered orally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 12 doses.

§ Six days after inoculation.

abdominally with a virulent strain of hemolytic streptococcus of Group A susceptible to both penicillin by intermittent intraabdominal injection and to sulfadiazine by ingestion treated with both compounds simultaneously (Table 2). Thus, of 20 mice given penicillin in total doses of 240 units per animal by intermittent intraabdominal injection, 14 (70%) survived, while of 20 given total doses of 12 mg. of sulfadiazine per animal by ingestion 2 (10%) survived; whereas of 20 given both compounds in these total dosages all (100%) survived, with 70% survivals among those given 120 units of penicillin with 12 mg. of sulfadiazine and 30% survival among those given 60 units of penicillin and 12 mg. of sulfadiazine.

Synergistic or additive effects were also observed in the treatment of mice inoculated intraabdominally with a virulent culture of Type I pneumococcus and treated with penicillin and sodium sulfadiazine (Table 3). Thus, of 20 mice given penicillin in total doses of 600 units per animal by intermittent intraabdominal injection, 8 (40%) survived, while of 20 given total doses of 40 mg. of sodium sulfadiazine by the same route of administration 5 (25%) survived; whereas of 20 given both compounds in these total dosages 18 (90%) survived, with 75% survivals among those given 120 units of penicillin and 40 mg. of sodium sulfadiazine and 45% survivals among those given 60 units of penicillin and 40 mg. of sodium sulfadiazine.

As previously stated, *Eber. typhosa* in small numbers has been found susceptible to relatively large amounts of penicillin and sodium sulfathiazole in the test-tube with synergistic or additive effects. As shown in Table 4, a culture of this bacillus inoculated intraabdominally in mice in an amount approximately equivalent to 2 minimal lethal doses was likewise susceptible to relatively large doses of penicillin and sodium sulfathiazole administered intraabdominally with definite evidence of synergistic or additive effects when the 2 compounds were injected simultaneously. Thus, of 20 mice given penic-

illin in total doses of 5000 units per animal by intermittent intraabdominal injection, 3 (15%) survived, while of 20 given total doses of 80 mg. of sodium sulfathiazole by the same route of administration 3 (15%) likewise survived; whereas of 20 given both compounds in these total dosages 8 (40%) survived with 25% survivals among those given 2000 units of penicillin and 80 mg. of sodium sulfathiazole and 20% survivals among those given 1000 units of penicillin and 80 mg. of sodium sulfathiazole.

As shown in Table 5, a culture of *Kleb. pneumoniae* virulent for mice by intraabdominal inoculation was susceptible to streptomycin sulfate and likewise to sodium sulfadiazine administered intermittently by intraabdominal injection. Thus, of 10 mice given streptomycin in total doses of 1.5 mg. per animal by intermittent intraabdominal injection, 3 (30%) survived, while of 10 given total doses of 75 mg. of sodium sulfadiazine by the same route of administration 2 (20%) survived; whereas of 10 given both compounds in these total dosages 8 (80%) survived with 60% survivals among those given 0.75 mg. of streptomycin and 75 mg. of sodium sulfadiazine and 20% survivals among those given 0.15 mg. of streptomycin and 75 mg. of sodium sulfadiazine.

The results observed in the treatment of 320 to 485 gm. guinea pigs inoculated subcutaneously with a human strain of *Myc. tuberculosis* and treated with streptomycin by intermittent subcutaneous or intramuscular injection, by diasone orally and by both compounds simultaneously have been previously reported;⁵ they are briefly summarized in Table 6 and clearly indicate some degree of synergistic or additive activity. The suppressive effects of these compounds as determined by the results of macroscopic and microscopic examinations of the tissues are not indicated in the table. On the basis of survival rates alone, however, it will be observed that 9 (50%) of 18 untreated controls survived while 7 (70%) of 10 animals given streptomycin in total doses of

TABLE 3.—SYNERGISTIC OR ADDITIVE ACTIVITY OF PENICILLIN AND SODIUM SULFADIAZINE IN THE TREATMENT OF EXPERIMENTAL TYPE I PNEUMOCOCCAL INFECTIONS OF MICE*

No.	Penicillin†		Sodium sulfadiazine‡		Survivors‡	
	Dose (units per mouse)	Total dosage (units per mouse)	Dose (mg. per mouse)	Total dosage (mg. per mouse)	No.	%
20	100	1200	20	100
20	50	600	8	40
20	10	120	6	20
20	5	60	2	10
20	10 0	80 0	12	60
20	5 0	40 0	5	25
20	50	600	5 0	40 0	18	90
20	10	120	5 0	40 0	15	75
20	5	60	5 0	40 0	9	45
20	Controls	0	0

* Inoculated intraabdominally with approximately 10,000 M.L.D. of culture.

† Administered intraabdominally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 12 doses.

‡ Eight days after inoculation.

TABLE 4.—SYNERGISTIC OR ADDITIVE ACTIVITY OF PENICILLIN AND SODIUM SULFATHIAZOLE IN THE TREATMENT OF EXPERIMENTAL EBER. TYPHOSA INFECTIONS OF MICE*

No.	Penicillin†		Sodium sulfathiazole‡		Survivors‡	
	Dose (units per mouse)	Total dosage (units per mouse)	Dose (mg. per mouse)	Total dosage (mg. per mouse)	No.	%
20	250	5000	3	15
20	100	2000	0	0
20	50	1000	0	0
20	4 0	80 0	3	15
20	250	5000	4 0	80 0	8	40
20	100	2000	4 0	80 0	5	25
20	50	1000	4 0	80 0	4	20
20	Controls	0	0

* Inoculated intraabdominally with approximately 2 M.L.D. of culture.

† Administered intraabdominally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 20 doses.

‡ Ten days after inoculation.

TABLE 5.—SYNERGISTIC OR ADDITIVE ACTIVITY OF STREPTOMYCIN AND SODIUM SULFADIAZINE IN THE TREATMENT OF EXPERIMENTAL KLEB. PNEUMONIAE INFECTIONS OF MICE*

No.	Streptomycin†		Sodium sulfadiazine‡		Survivors‡	
	Dose (mg. per mouse)	Total dosage (mg. per mouse)	Dose (mg. per mouse)	Total dosage (mg. per mouse)	No.	%
10	0 20	3 00	8	80
10	0 10	1 50	3	30
10	0 05	0 75	0	0
10	0 01	0 15	0	0
10	5 0	75 0	2	20
10	0 10	1 50	5 0	75 0	8	80
10	0 05	0 75	5 0	75 0	6	60
10	0 01	0 15	5 0	75 0	2	20
10	Control	0	0

* Inoculated intraabdominally with approximately 1000 M.L.D. of culture.

† Administered intraabdominally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 15 doses.

‡ Ten days after inoculation.

365 mg. survived, as likewise 3 (36.3%) of 8 animals given total doses of 192 mg. of this compound. Of 8 animals given total doses of 7.2 gm. of diasone by ingestion, 6 (75%) survived, while all of 8 animals given 168 mg. of streptomycin and 7.2 gm. of diasone survived.

served in the treatment of experimental syphilis of rabbits with single and multiple doses of penicillin by intermittent intramuscular injection;²³ also the synergistic effects of penicillin, mapharsen (oxophenarsine hydrochloride) and potassium bismuth tartrate in the treatment of this

TABLE 6.—SYNERGISTIC OR ADDITIVE ACTIVITY OF STREPTOMYCIN AND DIASONE IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS OF GUINEA PIGS

No.	Streptomycin, total dosage (gm. per animal)	Diasone, total dosage (gm. per animal)	Survivals	
			No.	%
10	0 365*	0	7	70 0
8	0 192†	..	3	36.3
8	..	7.2§	6	75.0
8	0 168†	7.2§	8	100.0
18	Controls	..	9	50 0

* Over 68 days by multiple intramuscular injection.

† Over 32 days by multiple intramuscular injection.

§ Over 32 days by oral administration.

As previously stated, the possible synergistic or additive effects of penicillin and streptomycin administered simultaneously in the treatment of pure and especially of mixed infections with bacteria susceptible to both compounds is of particular interest and clinical importance. To determine possible synergistic or additive effects *in vivo*, mice were inoculated subcutaneously with a virulent culture of *B. anthracis* which was found highly susceptible to penicillin and slightly susceptible to streptomycin *in vitro*. Animals were treated with penicillin and streptomycin alone by intermittent intraabdominal injection and likewise with freshly prepared solutions of each compound mixed together in the same syringe and injected intraabdominally. As shown in Table 7, of 20 mice given total doses of 3000 units of penicillin per animal, 14 (70%) survived, while of 20 given total doses of 5 mg. of streptomycin per animal, 2 (10%) survived; whereas of 20 given both compounds in these dosages, 18 (90%) survived, with 50% survivals among those given 1500 units of penicillin and 5 mg. streptomycin and 15% survivals among those given 750 units of penicillin and 5 mg. of streptomycin.

I have elsewhere described in detail the technique employed and the results ob-

servations in the treatment of experimental infection.²⁴ The results observed with single doses of penicillin by intramuscular injection and of mapharsen by intravenous injection are briefly summarized in Table 8 as, likewise, the results of combined treatment with single doses of each compound given at approximately the same time. It will be observed that single doses of penicillin as high as 100,000 units per kg. were not completely curative, as shown by the results of lymph node transfers to fresh animals. Mapharsen in single doses of 1 mg. per kg. were likewise not completely curative, whereas simultaneous treatment with single doses of 10,000 units of penicillin and 1 mg. of mapharsen per kg. effected complete or biologic cures, indicative of marked synergistic activity in confirmation of the results reported by Eagle, Magnuson and Fleischman.¹²

Similar results were observed with multiple doses of penicillin by intermittent intramuscular injection and of mapharsen by intravenous injection, summarized in Table 9. Total doses of 8000 and 40,000 units of penicillin and of 1.6 mg. mapharsen alone per kg. of weight did not effect complete or biologic cures, whereas total doses of 4000 and 8000 units of penicillin and 1.6 mg. mapharsen per kg. resulted in complete or biologic cures and likewise

TABLE 7.—SYNERGISTIC OR ADDITIVE ACTIVITY OF PENICILLIN AND STREPTOMYCIN IN THE TREATMENT OF EXPERIMENTAL *B. ANTHRACIS* INFECTIONS OF MICE*

No.	Penicillin†		Streptomycin†		Survivors‡	
	Dose (units per mouse)	Total dosage (units per mouse)	Dose (mg. per mouse)	Total dosage (mg. per mouse)	No.	%
20	250	7500	20	100
20	100	3000	14	70
20	50	1500	4	20
20	25	750	0	0
20	0 250	10 0	6	30
20	0 125	5 0	2	10
20	0 060	2 4	0	0
20	100	3000	0 125	5 0	18	90
20	50	1500	0 125	5 0	10	50
20	25	750	0 125	5 0	3	15
20	Controls	0	0

* Inoculated subcutaneously with approximately 5 M.L.D. of culture.

† Administered intraabdominally. First dose 2 hours after inoculation; thereafter every 6 hours for a total of 30 doses. When given conjointly solutions of each compound were freshly mixed and promptly injected.

‡ Twelve days after inoculation.

TABLE 8.—SYNERGISTIC OR ADDITIVE ACTIVITY OF SINGLE DOSES OF PENICILLIN AND MAPHARSEN IN THE TREATMENT OF ACUTE SYPHILITIC ORCHITIS OF RABBITS

No.	Penicillin* (units per kg.)	Mapharsen† (mg. per kg.)	Results of lymph node transfers
2	10,000	..	Both positive
2	30,000	..	" "
2	100,000	..	" "
2	..	1	" "
2	10,000	1	Both negative
2	Controls	..	Both positive

* By intramuscular injection in saline solution.

† By intravenous injection.

TABLE 9.—SYNERGISTIC OR ADDITIVE ACTIVITY OF MULTIPLE DOSES OF PENICILLIN AND MAPHARSEN IN THE TREATMENT OF ACUTE SYPHILITIC ORCHITIS OF RABBITS

No.	Penicillin		Mapharsen*		Results of lymph node transfers
	Dose (units per kg.)	Total dosage (units per kg.)	Dose (mg. per kg.)	Total dosage (mg. per kg.)	
2	1000*	8,000	Both positive
2	5000*	40,000	" "
2	0 2	1 6	" "
2	250†	4,000	0 2	1 6	Both negative
2	500†	8,000	0 2	1 6	" "
2	Controls	Both positive

* Once daily for 8 days in succession intravenously (8 doses).

† Twice daily for 8 days in succession intramuscularly (16 doses).

‡ Once daily for 8 days in succession intramuscularly (8 doses).

clearly indicative of the marked synergistic activity of these 2 compounds

As shown in Table 10, multiple doses of penicillin by intermittent intramuscular injection totalling 8000 and 40,000 units, and of potassium bismuth tartrate in oil by intramuscular injection totalling 2 mg. per kg. did not result in complete or bio-

logic cures, whereas injections of penicillin in total doses of 8000 and 16,000 units and of potassium bismuth tartrate in total doses of 2 mg. per kg. of weight resulted in complete or biologic cures; being clearly indicative of the synergistic or additive activity of these 2 compounds.

Exactly similar results were observed

with multiple doses of mapharsen by intravenous injection and of bismuth subsalicylate in oil in the treatment of acute syphilitic orchitis of rabbits. This experiment was conducted in exactly the same manner as the experiment employing penicillin and potassium bismuth tartrate. As shown in Table 11, mapharsen by intravenous injection in total doses of 1, 2 and 4 mg. per kg. did not produce complete or biologic cures and the same was true of bismuth subsalicylate by intramuscular injection in total doses of 1.25, 2.5 and 5 mg. per kg. In combined treatment, however, mapharsen in total doses of 2 and 4 mg. and bismuth subsalicylate in total doses of 2.5 and 5 mg. per kg. resulted in complete or biologic cures.

SYNERGISTIC OR ADDITIVE ACTIVITY OF COMPOUNDS IN THE TREATMENT OF HUMAN INFECTIONS. Much fewer data of a precise

nature are available for appraising the status of synergistic or additive activity of chemotherapeutic compounds in the treatment of various acute and chronic infections of man. There are, however, numerous reports indicating the value of the combined therapy of pneumococcal pneumonia with sulfadiazine or sulfamerazine and penicillin and especially in the treatment of serious cases of the disease. In general terms the reported mortality rates in cases treated with the sulfonamide compounds alone have been as low and even somewhat lower than in cases treated with penicillin alone. That combined treatment with sulfadiazine and penicillin may give better results than treatment with sulfadiazine alone is indicated, however, by the report of Dowling and his associates,¹⁰ who observed a mortality of 9.6% in 94 cases treated with sulfadiazine

TABLE 10.—SYNERGISTIC OR ADDITIVE ACTIVITY OF MULTIPLE DOSES OF PENICILLIN AND POTASSIUM BISMUTH TARTRATE IN THE TREATMENT OF ACUTE SYPHILITIC ORCHITIS OF RABBITS

No.	Penicillin*		Potass. bismuth tartrate†		Results of lymph node transfers
	Dose (units per kg.)	Total dosage (units per kg.)	Dose (mg. per kg.)	Total dosage (mg. per kg.)	
2	1000	8,000	Both positive
2	5000	40,000	" "
2	0.5	2.0	" "
2	1000	8,000	0.5	2.0	Both negative
2	2000	16,000	0.5	2.0	" "
2	Controls	Both positive

* Once daily for 8 days in succession intramuscularly (8 doses).

† Four doses given on the 2nd, 4th, 6th and 8th days of treatment, intramuscularly.

TABLE 11.—SYNERGISTIC OR ADDITIVE ACTIVITY OF MULTIPLE DOSES OF MAPHARSEN AND BISMUTH SUBSALICYLATE IN THE TREATMENT OF ACUTE SYPHILITIC ORCHITIS OF RABBITS

No.	Mapharsen*		Bismuth subsalicylate†		Results of lymph node transfers
	Dose (mg. per kg.)	Total dosage (mg. per kg.)	Dose (mg. per kg.)	Total dosage (mg. per kg.)	
2	0.8	8.0	Both negative
2	0.4	4.0	Both positive
2	0.2	2.0	" "
2	0.1	1.0	" "
2	2.00	10.00	Both negative
2	1.00	5.00	1 positive
2	0.50	2.50	1 negative
2	0.25	1.25	Both positive
2	0.4	4.0	1.00	5.00	" "
2	0.2	2.0	0.50	2.50	Both negative
2	" "
2	0.1	1.0	0.25	1.25	1 positive
2	Controls	1 negative
2	Both positive

* Twice weekly for 5 weeks by intravenous injection (10 doses).

† Once weekly for 5 weeks by intramuscular injection (5 doses).

alone but only 4.3 % in 94 cases treated with sulfadiazine and penicillin. Combined treatment with penicillin and sulfadiazine has also been found of inestimable value in the treatment of putrid lung abscess by Stivelman and Kavee,⁴² aside from the fact that it has been widely employed for the prevention of infections following resections of the lungs, transurethral prostatectomies, in the treatment of pilonidal cysts by primary closure, and others.

In pneumococcal meningitis treated with the sulfonamide compounds alone the reported mortality rates have varied from 58 to 65 %, with a mortality rate of about 48 % in cases treated with penicillin alone. Waring and Smith,⁴⁶ however, have reported the recovery of 12 out of 13 patients following combined sulfonamide and penicillin therapy. Similar results have also been reported by Smith, Duthie and Cairns.³⁸ Of 19 cases treated with penicillin alone there were 7 deaths, whereas in 19 cases treated with penicillin and sulfadiazine there were but 2 deaths, 1 of whom recovered from the meningitis but died subsequently of fat embolism, while the second case was moribund on admission to the hospital and died within a few hours. Hall and his associates¹⁶ have also reported the recovery of 13 in a series of 17 cases of pneumococcal meningitis, 16 of whom were treated with sulfadiazine or sulfamerazine in addition to penicillin, while 2 of 3 infants with staphylococcal meningitis recovered under the combined penicillin and sulfonamide therapy.

Until recent years the mortality rate in influenzal meningitis treated with the sulfonamide compounds alone was about 92 %. Alexander and her associates,¹ however, have recently reported the recovery of 12 in a series of 14 cases treated with streptomycin with the recovery of all of 4 additional cases treated with the compound after initial treatment with Type B rabbit anti-influenzal globulin and sulfadiazine; likewise, the recovery of 3 out of 4 patients treated with streptomycin

after unsuccessful treatment with the anti-serum and sulfadiazine. Nussbaum and his colleagues³⁵ have also reported the rapid and complete recovery of 3 children with influenzal meningitis treated concurrently with streptomycin and sulfadiazine, while Logan and Herrell²⁹ have reported the recovery of 3 out of 4 infants treated with streptomycin, sulfonamides and anti-serum. In streptococcal meningitis treated with the sulfonamide compounds alone the mortality has been about 35 %, with a mortality of about 44 % in cases treated with penicillin alone; whether or not combined treatment with sulfadiazine and penicillin will result in a further reduction in the mortality rates cannot be stated, but this combined therapy appears to be indicated in the treatment of severe infections. The same may be true in the treatment of meningococcal meningitis, even though the mortality under prompt and adequate sulfonamide therapy may be less than 10 %, and about 12 % in cases treated with penicillin alone.

Whether or not combined penicillin and sulfonamide therapy is better than penicillin alone in the treatment of subacute bacterial endocarditis cannot be stated at the present time. Under sulfonamide treatment alone the mortality rate has been about 96 %, with a mortality of from 40 to 45 % in cases adequately treated with penicillin. In the combined treatment of 7 cases with penicillin and sulfadiazine, with or without heparinization, Levy and McKrill²⁸ have reported the death of 2 patients, giving a mortality of 28.6 %. Certainly this combined treatment appears to be clearly indicated in the treatment of acute endocarditis due to infections with beta-hemolytic streptococci, staphylococci, pneumococci, gonococci and meningococci, while in infections due to *H. influenzae*, *Klebs. pneumoniae* or other gram-negative bacilli combined treatment with streptomycin and sulfadiazine appears to be worthy of clinical trial.

As previously stated, Bigger has observed a synergistic or additive activity of sulfathiazole and penicillin for typhoid

bacilli *in vitro*, while, as previously stated, I found some evidence of this activity in the treatment of experimental typhoid infections of mice. Whether or not combined treatment of typhoid fever of man with very large doses of penicillin and sulfathiazole will prove effective cannot be stated at the present time, although McSweeney³⁴ has recently reported this combined treatment as being successful in 6 cases. Comerford and his associates⁹ have also found this combined therapy effective in the treatment of 2 typhoid carriers. Whether or not the treatment of these typhoid infections with streptomycin and sulfathiazole will prove more effective than treatment with streptomycin alone is well worthy of experimental and clinical investigation.

Whether or not the combined treatment of tuberculosis with streptomycin and the sulfone compounds will prove more effective than treatment with streptomycin alone awaits the outcome of clinical experience. In this connection it appears that promin and diasone may be too toxic from the standpoint of producing hemolytic anemia. However, promizole is much less toxic and apparently the compound of choice. O'Leary and his associates³⁶ found promizole alone of but little value in the treatment of various types of cutaneous tuberculosis; streptomycin was more effective but combined treatment with both compounds was not employed.

Insofar as combination chemotherapy in syphilis is concerned, most interest has been in its effectiveness in the treatment of early cases of the disease. Eagle¹¹ has reported that tri-weekly injections of mapharsen with weekly injections of bismuth were highly effective with 82% "cures" and but 9.3% treatment failures. Excellent results in the treatment of early syphilis have also been reported by Sternberg and Leifer¹⁴ by a plan of treatment embracing 40 injections of mapharsen and 16 of bismuth subsalicylate over a period of 26 weeks. Bundesen,⁴ however, regards the rapid treatment of early syphilis by

the combined administration of penicillin and mapharsen as unsatisfactory. Heller¹⁵ has likewise reported that there is no significant difference in results in the treatment of early syphilis with penicillin alone and smaller doses of penicillin along with mapharsen, although it appeared that the curative activity of penicillin was enhanced by the conjoint administration of bismuth. In a comparative study of 5 different plans of combination treatment of early syphilis Leavitt²⁵ states that best results were observed following the administration of 5 doses of mapharsen and 3 of bismuth along with 1,200,000 units of penicillin by intermittent intramuscular injection every 3 hours over a period of 9 days.

As previously stated, it would appear that penicillin and bacteriophage also exert synergistic or additive effects against staphylococci *in vitro* and in this connection MacNeal and his associates^{30,31,32} have reported the successful treatment of cases of staphylococcal endocarditis and septicemia by combined treatment with these agents, even though the staphylococci were highly resistant to penicillin and bacteriophage alone *in vitro*.

TOXICITY OF COMBINED CHEMOTHERAPY. Objections may be raised to combined chemotherapy on the basis of toxic reactions. But this hardly appears to be justified. Certainly there have been no indications of increased toxicity in the treatment of experimental infections of the lower animals. Indeed, it would appear that the reverse is true, since the smaller doses of each of the compounds employed are usually less than of either compound alone. Some cases of hemorrhagic encephalitis due to mapharsen have been reported in the treatment of early syphilis with this compound in combination with penicillin by intensive methods, but the incidence has been lower than observed with mapharsen alone because of the smaller total dosages employed in the combined methods of treatment. Indeed, if a sulfone compound like promizole in combination with strepto-

mycin is found upon clinical trial to be helpful in the treatment of tuberculosis, it is possible that smaller total doses of the latter may not only be employed with a reduction in the incidence of both reversible and irreversible injury of the labyrinth and auditory nerves resulting in tinnitus and vertigo, but possibly reduce the chances of so-called acquired resistance of tubercle bacilli to streptomycin as well.

In this connection it should also be stated that Lehr^{26,27} has observed that mixtures of sulfadiazine and sulfamerazine, and of these 2 compounds with sulfathiazole in partial dosages, proved significantly less toxic for albino rats than any one of the separate compounds in equal or comparable total dosage, the lower toxicity of the combinations being ascribed to the prevention of renal obstruction resulting from a pronounced reduction in the intratubular deposition of sulfonamide crystals.

Summary. 1. Combinations of the chemotherapeutic compounds have usually shown synergistic or additive effects

upon susceptible microorganisms *in vitro*. Such combinations have also shown evidence of preventing so-called acquired resistance of microorganisms *in vitro* with the suggestion that combination chemotherapy may reduce the incidence of so-called acquired resistance of bacteria in the treatment of disease.

2. Undoubtedly the combination chemotherapy has shown evidence of synergistic or additive activity in the treatment of various bacterial and spirochetal infections of the lower animals.

3. Synergistic or additive chemotherapy has also proven of sufficient value in the prevention and treatment of various serious bacterial infections of human beings and, possibly, also of early syphilis, as to merit further clinical trial.

4. The possibility of toxic reactions is not necessarily a contraindication to combined chemotherapy; on the contrary, it appears that such treatment may reduce their incidence by reason of the smaller total dosages required than of either compound alone.

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MORPHOLOGIC STUDIES OF THE INTESTINE IN SALMONELLA INFECTION IN GUINEA PIGS AND MICE

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THE pathologic experience with 9 autopsies of patients dying with sporadic salmonella infection at the Queens General Hospital during a 4-year period is presented in a separate communication,¹ with bacteriologic and clinical correlation. A total of 13 deaths were encountered in 86 cases of sporadic salmonellosis, with 21 different organisms. The 3 most common organisms were *S. cholerae suis*, *S. typhi murium* and *S. orientienburg*, with 11, 20 and 16 instances respectively. In general, the infections with *S. orientienburg* were mildest, with localization in the gastro-intestinal tract, or were completely asymptomatic. The infections with *S. cholerae suis* were most severe, with a septic picture and bacteremia predominating, with and without seeding foci (Seligmann, Saphra and Wassermann¹⁶).

The cases of *S. typhi murium* infection occupied an intermediary position between these 2 other organisms, with both gastro-intestinal localization and a typhoid-like picture occurring as often as mild or asymptomatic cases, and an occasional septic picture. Our autopsy experience emphasizes the parallelism of *S. typhi murium* infection to typhoid infection, with its mutable multifarious syndromes. In the 9 autopsied cases, there were 3 deaths due to *S. cholerae suis*, and 3 due to *S. typhi murium*. The remaining 3 necropsies showed *S. newport*, *S. montevideo* and *S. lichtfeld*, with variable pictures described elsewhere. Study of the recorded 17 deaths due to *S. typhi murium*, on

file at the Beth Israel Hospital National Salmonella Center in New York City, rendered available through the kindness of Dr. Seligmann, confirms the mimicry of typhoid, with gastro-intestinal, septic, pulmonary, febrile and cerebral variations in symptomatology. Study of the data of the 9 cases coming to autopsy in this group confirms this impression.

The broad biologic problem of variation, adaptation and reactive tissue changes in different hosts seemed best studied with this organism. With this in mind, we undertook the study of the morphologic reaction in guinea pigs and mice with various strains of *S. typhi murium*, using other salmonella as controls. We desired to establish an explanation for the histiocytic typhoid-like reaction and the remarkable localization of the lesions in Peyer's patches of the intestine, and to attempt the controlled experimental reproduction of this lesion of the intestinal Peyer's patches in the animal.

Our interest in this subject was stirred by the autopsy in 1941 (Grier) which showed the typical morphologic gross and microscopic picture of typhoid fever. The organism cultured from several foci was *S. typhi murium*. A few months later, another patient was admitted with a clinical picture of typhoid fever, and showed this same organism in his blood stream. At autopsy, the second case failed to show the characteristic hyperplastic lesions in the Peyer's patches, though the mesenteric lymph nodes were hyperplastic. The

only other instance in which hyperplastic Peyer's patches were found at autopsy represented an infection with *S. cholerae suis*. This 9 year old child showed also a chronic cholangitis with biliary cirrhosis. Another autopsy, with clinical picture of convulsions and coma with high temperature, also showed hyperplasia of Peyer's patches and mesenteric lymph nodes, and yielded *S. typhi murium* from blood, lung and stool. The remaining autopsies showed no morphologic alteration in the gastro-intestinal tract. The only instance in the literature in which the typhoid-like morphology was adequately described in salmonella infections in the human was a single instance in a group of 4 deaths due to "paratyphoid Breslau" (old terminology for *S. typhi murium*), recently reported by Neessen and Meckel.⁷

Material and Methods—Animal Group 1.

It was felt originally that this tendency to localization in the Peyer's patches in the intestine might be accounted for on the basis of strain variation. To test this hypothesis, several strains of *S. typhi murium* were fed to laboratory animals; at first guinea pigs, rats and mice, and then only guinea pigs and mice. In all, 6 strains of *S. typhi murium* were used for this purpose (Grier, Thomas, 1182 B. I., Kaufman B. I., 43930 N. Y. Lab., Williams). A total of 53 guinea pigs, 15 mice and 3 rats were studied by means of serial sacrifice using the strains specified. The dosage of organisms given was a minimum of 0.5 cc. to mice, 2 cc. to rats and 3 cc. to guinea pigs of a 24 hour broth culture. Anal swab cultures were taken routinely to rule out any preëxisting salmonella infection.

The tissues were removed immediately upon sacrificing the animals, cultured, and put in formalin and in Zenker's formal fixative. The organisms were recovered from the exact sites that presented the tissue changes in most animals. They were embedded in paraffin, cut at 6 μ , and stained with hematoxylin and eosin, Goodpasture, Giemsa and MacCallum stains. The sacrifice time varied from 24 hours to 12 days, and animals were killed when obviously ill. In the fixation, particular pains were taken to obtain quick action by

cutting thin slices of solid organs and injecting the fixatives into the lumen of the bowel to the point of distention, and then ligating the fixative *in situ*, followed by immersion in a minimum of 20 volumes of the fixing solution.

FINDINGS AND INTERPRETATION. The initial group of guinea pigs fed the strain of organism obtained from the initial *S. typhi murium* case (Grier) showed remarkable localization of involvement in the region of the Peyer's patches and the mesenteric lymph nodes, in contrast to some of the other organisms.

The findings in the remaining viscera corresponded to the usual typhoid-like visceral lesions. These original observations have not been corroborated and have been corrected by subsequent experiments in guinea pigs, which showed that several of the salmonella strains (*S. typhi murium*, Kaufman B. I., *S. enteritidis*, and the *S. typhi murium* strain from the second case, Thomas which failed to show localized lesions in the lymphoid tissue of the human gut) can produce such lesions.

The guinea pig seems best adapted for the study for such localizing lesions with *S. typhi murium*, though the mouse shows this identical tendency with the enteritidis organisms and occasionally with a typhi murium strain. The Peyer's patches in the guinea pig are easily observed for early changes. Possibly the guinea pig has a degree of resistance which seems to favor such localization in Peyer's patches. Very few morphologic studies of salmonella infection in guinea pigs are available. Duthie and Mitchell⁴ found early miliary tubercle-like lesions in the viscera with only a few cases showing swelling and grayish appearance in Peyer's patches. The morphologic changes in the rat and the mouse have been studied, particularly by Waldman and Rostow,²¹ but the changes in the guinea pig have been neglected. Most authors have dealt with the bacteriologic and serologic aspects of this problem (Ørskov and co-workers,^{2,3,11} and Seifert and his co-workers,¹¹ and others).

The morphologic lesions were studied by serial sacrifice of animals at 24, 48 and 72 hours, and then at 6, 7, 10, 12 days and later. Changes were found with different strains at different times. With the original Grier strain, changes were found within 24 hours, and well developed alterations of Peyer's patches within 48 hours. Some of the illustrations will demonstrate the varying stages of evolution of the alteration in the Peyer's patches

(Figs. 1, 2, 3 and 4). Areas of catarrhal exudate appear in isolated crypts in the Peyer's patches with a few polymorphonuclears and monocytes present. Large mononuclear cells appear in Peyer's patches proper, focally and diffusely. Polymorphonuclear exudate appears at the margin of lymph follicles or beneath the epithelium. The polymorphonuclear cells accumulate to form micro-abscesses; these erode through the epithelium and give

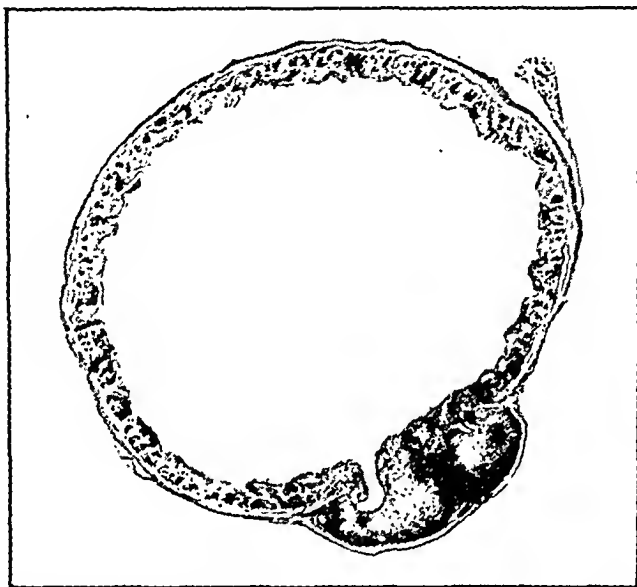


FIG. 1.—Cross-section of lower small intestine through Peyer's patch of guinea pig, showing marked involvement with a tendency to localization in Peyer's patch.

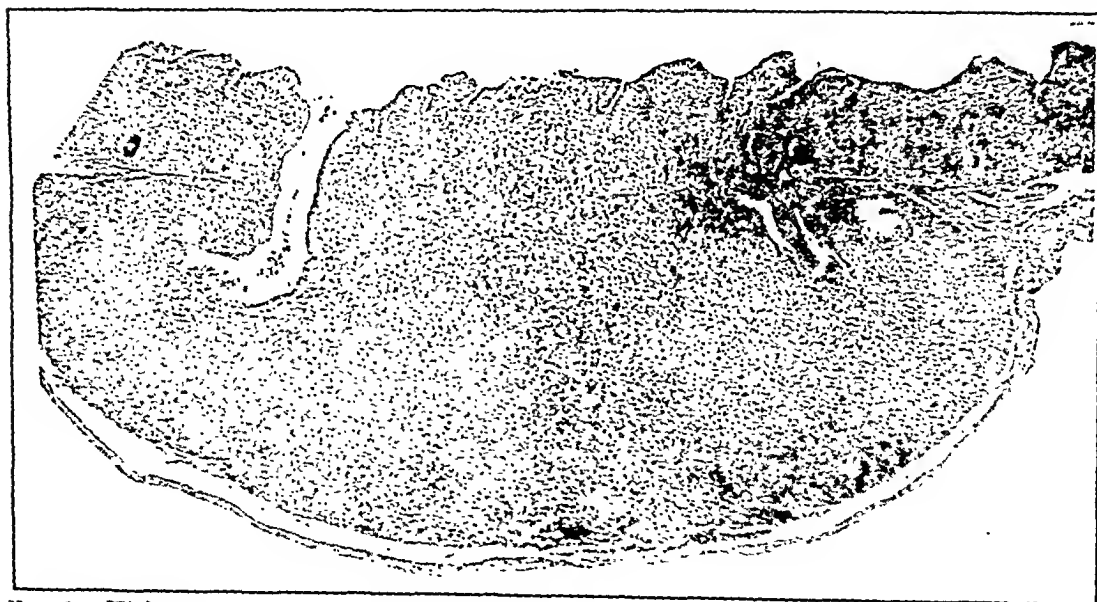


FIG. 2.—Higher magnification of Peyer's patch, showing prominent mononuclear character of most of the exudate with some micro-abscesses just penetrating into the lumen.



FIG. 3.—A mononuclear focus with a micro-abscess in a Peyer's patch, discharging into the lumen.

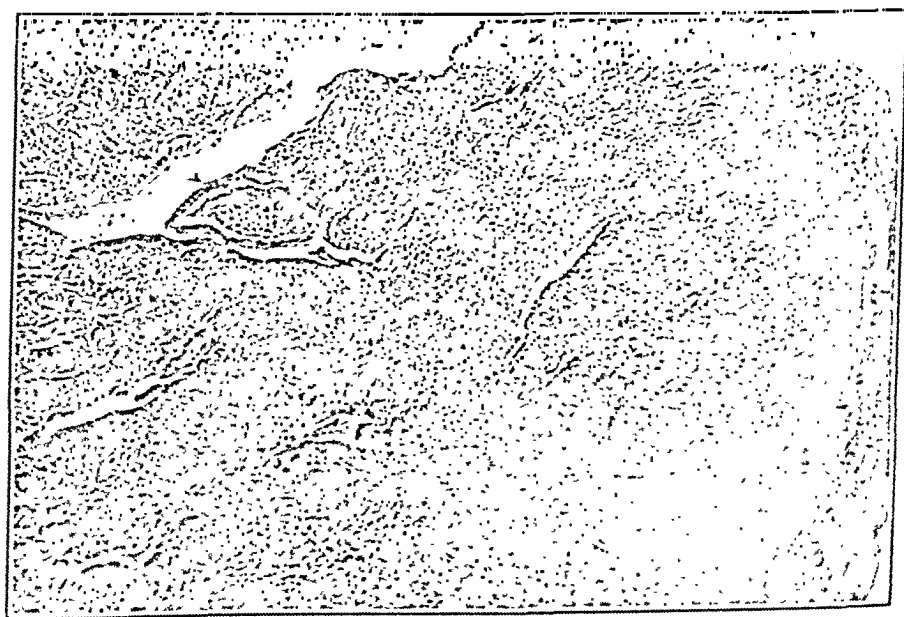


FIG. 4.—A micro-abscess with a peripheral differentiated mononuclear reaction.

rise to ulceration, with a fibrinocellular exudate on the surface. In the later stages, polymorphonuclear cells are particularly prominent. In the earlier stages monocytes, or the histiocytes so characteristic of typhoid reaction, are prominent. Typhoma-like nodules were seen in the Peyer's patches and in the mesenteric lymph nodes.

The distribution of bacteria was studied in the varying stages of invasion and evolution of the lesion. We could not

of the mesenteric nodes was noted. A labilization of monocytes in the sinusoids and a proliferation of reticulum cells in the lymph node proper occurred rapidly (Fig. 5) and in considerable abundance. The tendency to focal necrosis and micro-abscess was a bit more marked in the lymph node. Occasionally tubercle-like structures, with maturation of monocyte cells to give an epithelioid appearance, with and without central necrosis or micro-abscesses and giant cells, were seen

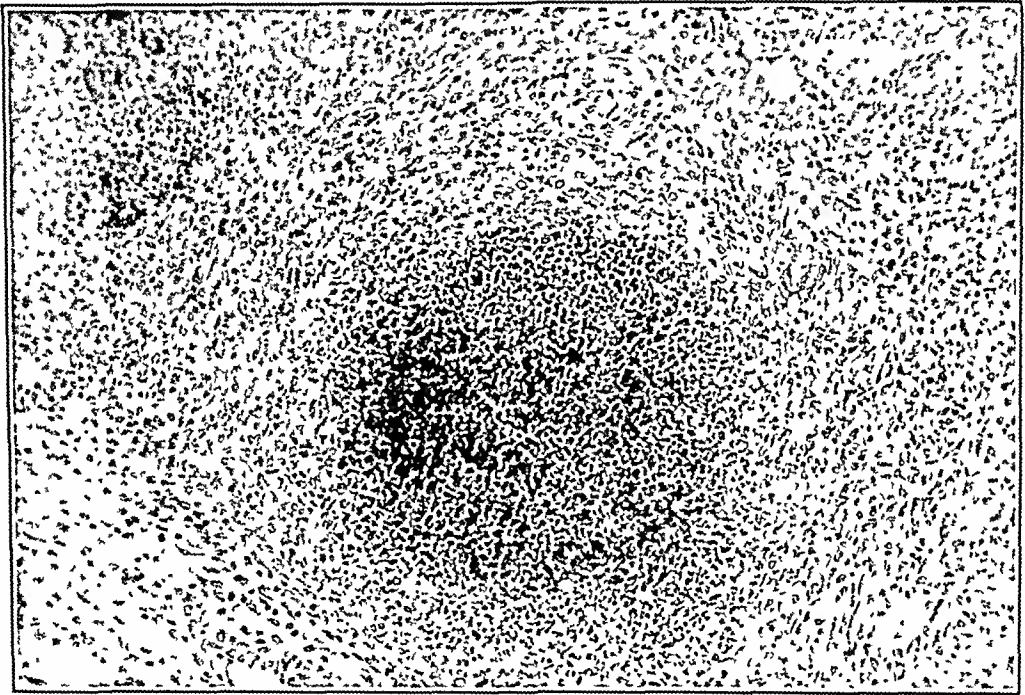


FIG. 5.—Higher magnification, showing epithelioid character to the peripheral mononuclear exudate.

confirm the work of Goodpasture⁶ as to the intracellular symbiosis of the organism with the plasma cell or the monocyte. The organism was found as frequently in polymorphonuclear cells as in monocytes, and was often seen between the cells in the early and late stages. Goodpasture's observation that the epithelium was resistant to bacterial invasion would seem definitely confirmed. The epithelium never showed organisms unless overgrown. This in the main agrees with the findings of Florey.⁵

Throughout the above changes in the Peyer's patches, a parallel transformation

(Fig. 6). Acid-fast stains were negative. The resemblance to the "typhoid reaction" in the human was compelling.

DISCUSSION. It was thought originally that the histologic response observed might be due to a peculiarity of the antigenic structure of *S. typhi murium*. It was felt that possibly the XII somatic antigen, of the Kaufman-White schema, which *S. typhi murium* has in common with the typhoid group of organisms, might be accountable for this type of reaction, in the same sense as the chemical fractions of the tubercle bacillus have yielded specific morphologic reactions. This seemed

at first to be borne out by the finding of similar lesions with 2 strains of enteritidis, which organisms possess the XII somatic antigen, and the parallel failure of the infection with *S. muenchen* and *S. lichtfeld*, both of which strains do not possess the somatic antigen XII, to give such localized lesions in the ileum. The latter observations need verification, because a total of only 6 guinea pigs were used for the *lichtfeld* strain and 3 for the *S. muenchen*. It is our impression that in any series of animals injected with strains

matter further, for collateral evidence given below seemed to rule out its significance.

The failure of Waldman to produce lesions in Peyer's patches in mice with *S. schottmuelleri* (para B) which also possesses somatic XII antigen, as does *S. enteritidis* which produced the lesion in as high as 80% of the mice, seemed contrary to the intimation of this interpretation of these experiments. Also Pike and MacKenzie,¹² Pike and Swinney,¹³ Boivin,^{2,3} and others have indicated that the major determinant

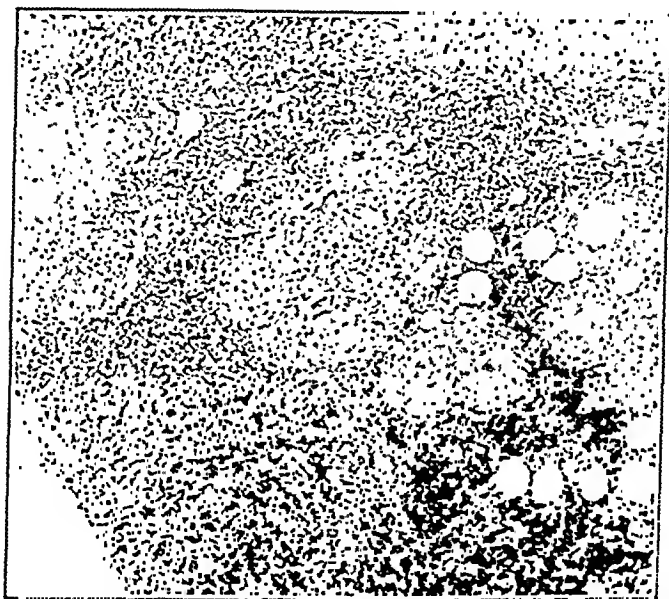


FIG. 6.—Epithelioid and tubercle-like response in the mesenteric lymph nodes. Note the giant cells present.

of *S. typhi murium* or other salmonella organisms, a group of 6 animals might be found which will fail to give the localizing reaction in the Peyer's patches. Pike and MacKenzie¹² have shown that large differences in virulence of strains will not be apparent, if tested in highly susceptible animals over a narrow range of doses, and this presumably applies to the morphologic reaction. A larger series of animals should be used before ruling out any particular type of morphologic reaction or giving a commanding position to any one demonstrated variant of tissue response. We have not pursued this

of virulence and infectivity of some members of the salmonella group is serologically negative. Dr. Saphra informs me that no antigenic component, including the Vi factor, is definitely associated with pathogenicity in his experience. The possibility that a particularly high titer of somatic XII antigen in the Grier strain might be significant was considered. This was ruled out by Dr. Seligmann and Dr. Saphra, who observed that the Grier strain, which gave us our best localization in Peyer's patches, showed, if anything, a lower titer of the somatic XII component. The mechanism involved in the produc-

tion of such localization still remains obscure. Waldman and Rostowa have indicated that the lesion in the gastrointestinal tract bears no relationship to the number of organisms in the gastrointestinal lumen, as determined by counts on seeded plated media. They stress the fact that the localization of the lesion depends on more than the lumen of the tract. It is of interest that in agreement with the latter authors, the cases that demonstrated the lesions best in Peyer's patches were cases in which the organism was placed directly into the mouth of the animal, preferably in food. Intraperitoneal injection failed to give localizing lesions in Peyer's patches, as has been amply demonstrated already by others for the subcutaneous and intravenous route. The avenue of infection would seem to be significant.

The Peyer's patches and the draining mesenteric node, so prominent in this localized typhoidal form of enteric disease, occupies the same position as the primary complex in tuberculosis. The work of Örskov,^{9,10,11} and his associates, and that of Seiffert,¹⁴ Takita,¹⁸ Müller,⁸ Waldman,¹⁹ and others, has shown that the organisms are disseminated soon after ingestion and leave the intestinal tract, only to appear again later, much as was shown to occur with the primary complex in tuberculosis by Krause and others, except for the fact that the peripheral component of the primary complex of tuberculosis does not present the multiple involvement of many Peyer's patches. It must be remembered that tremendous numbers of salmonella organisms were given in contrast to what obtains ordinarily in the instance of the usual single satellite lesion of the ordinary intestinal tuberculous primary focus.

We are left with no adequate positive explanation for the localizing reaction. The thought remains that it might follow from the degree of the imbalance *in toto* of the virulence of the particular organism (Wilson²²), to the local and general resistance of the host as a whole. With this

in mind, we repeated a series of guinea pigs with a very virulent type of organism given to us by Dr. Seligmann (1898).¹⁶ This virulent strain also did give very characteristic lesions in Peyer's patches and in the mesenteric lymph nodes. The findings in this group of animals were, if anything, a bit more pronounced, though slower in appearance, than that obtained with the original Grier strain. The inability to produce such localized lesions on occasions, in some groups of guinea pigs with the same organisms which did cause such lesions in other pigs, indicates that the factors of individual variation and immunity are also of considerable importance.

Materials and Methods—Animal Group 2. To test the hypothesis that the localized typhoid-like lesions of the intestinal tract, with their characteristic labilization of monocytes was dependent upon the degree of imbalance between the virulence of the organs and the local and general resistance of the host as a whole, 25 mice, 11 rats and 14 guinea pigs were fed the same virulent organism in identical dosage of 24 hour culture, *i. e.*, 0.5 cc. to mice, 2 cc. to rats and 3 cc. to guinea pigs, and treated thereafter with streptomycin. The streptomycin was given in saline solution to some and to others in oily suspension to prolong the effect by delayed absorption. Blood levels were not determined. No endeavor to obtain cures of the infected animals was made. We wished to observe morphologic alterations at various time intervals, and all animals were sacrificed at periods varying from 6 to 96 hours after infection. The time selected was determined by the known tendency of untreated animals to show such lesions. The mice were given 100 units orally and 500 units per 20 gm. subcutaneously; the rats were given 700 units orally and 300 units per 10 gm. subcutaneously; the guinea pigs were given 1500 units orally and 500 units per 20 gm. subcutaneously. The subcutaneous dose was trebled when the animals were allowed to live from 24 to 72 hours (3 mice, 3 rats and 4 guinea pigs) and the dose was multiplied by 5 for the single animal of each type, which was allowed to live for 96 hours. Again tremendous

doses of organisms were administered, a minimum of 0.5 cc. of a 24 hour broth culture being used.

FINDINGS AND INTERPRETATION. All 3 animal species did present the most consistent and outstanding localized lesions in Peyer's patches that had been obtained in any single series up to this time. The localized lesions in the Peyer's patches were prominent and well established in the mice and rats as well as the guinea pigs, which finding was noted only occasionally in untreated injected animals in these smaller species. It would seem that the therapeutic benefit of streptomycin tipped the balance in favor of the host, and a more favorable balance for localization of a primary type of infection was obtained. It is of interest that no definite evidence of healing was noted. This would be in keeping with the work of Seligman and Wassermann,¹⁷ who found that the antibiotic rendered the tract free of organisms and delayed mortality only. As soon as the antibiotic was withheld, the organism reappeared in the tract and interest further that on the basis of general pathology of the salmonella infection in experimental animals, it was decided that both oral and subcutaneous administration of the streptomycin was indicated. It would seem that with the doses used for the time interval studied, the infection is held in check sufficiently to give the characteristic morbid changes and that no evidence of cure in the ordinary sense or healing of the lesion was encountered. At the time this work was done, streptomycin was difficult to obtain, and only a sufficient amount could be gotten for this relatively small series of animals. This work is to be repeated with a larger series, and it is hoped to test this hypothesis further with animals which have been given a partial immunity by vaccination.

Conclusion. The morphologic changes of salmonella infection in the Peyer's patches of the intestine of guinea pigs

are traced through the various stages from early invasion with histiocytosis to necrosis, micro-abscesses and ulceration. The early lesion is studied from the standpoint of morphologic demonstration of bacterial invasion.

The attempt to establish an explanation for the histiocytic reaction and the localization in Peyer's patches, and the typhoid-like morphologic response, on the basis of antigenic component structure of the *S. typhi murium*, by the use of different antigenic strains of salmonella, has been unsuccessful. This indication of our morphologic studies parallels the work of others as to the relative lack of significance of component antigenic structure in respect to bacteriologic, morbidity and mortality studies in this field.

It is thought that the method of administration, the virulence of the organism, and the local and general resistance of the particular animal species, as well as the individual variation of the host, may represent important factors in the mechanism of pathologic localization to determine the characteristic morphologic lesions, and particularly the unique localization and distortion of Peyer's patches of the intestine. It is thought that the local tissue interrelationship that follows from the degree of imbalance between the virulence of the particular organism *in toto*, rather than the antigenic structure, and the local and general resistance of the host as a whole, may be the determinant of the typhoid-like reaction. The outstanding histiocytic reaction with the monocytic proliferation, giving the typhoid-like appearance of Peyer's patches, which followed with infection plus the administration of streptomycin to favor the host, seems to confirm this viewpoint.

The localizing reaction in the Peyer's patches and the regional lymph nodes presents several features of similarity to the better-known primary complex in tuberculosis, with peripheral focus and satellite lymph node localization in mesenteric nodes.

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THROMBOPLASTIC FACTORS IN THE ESTIMATION OF PROTHROMBIN CONCENTRATION

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THE increasing popularity of anticoagulant therapy has led to extensive clinical use of dicumarol, a drug whose therapeutic effect is achieved by reduction of the plasma prothrombin concentration. Safe and effective administration of this agent is entirely dependent upon repeated quantitative determinations of the plasma prothrombin content. The only available method for this measurement suitable for routine clinical application is the Quick test⁹ or one of its modifications. In this test prothrombin concentration is estimated by measuring the rate at which oxalated plasma clots at body temperature after addition of thromboplastic substance and calcium. Unfortunately, the clotting time is influenced not only by the amount of prothrombin present but also by other plasma components, by the concentration of the solution used for recalcification, and particularly by the nature of the thromboplastin employed.² When a standard technique is used, a hyperbolic relationship exists between clotting time and prothrombin concentration.⁹ However, the form of the hyperbola is extremely variable and is determined by the nature of the thromboplastin, the calcium concentration, and the nature of the substrate in which the prothrombin is dissolved. Expression of the result of a prothrombin test in terms of "prothrombin time" is therefore meaningless unless the exact method used and the curve depicting the relationship between prothrombin time and prothrombin concentration for that

particular method are known. The expression of the result of the test in terms of its relationship to the clotting time of a normal plasma, the so-called "prothrombin index," is equally without meaning. Two very similar thromboplastins which give the same clotting times for a normal plasma may give very different results for an abnormal plasma.⁷

There is no agreement on the proper method of standardizing the prothrombin test, although the necessity for careful standardization is now fully appreciated.^{1,7}

In order to make the test quantitative, most investigators compare an unknown plasma with that dilution of a normal plasma which gives the same clotting time, expressing the result in terms of % of the normal prothrombin concentration. That this method is satisfactory for clinical use is suggested by the fact that large numbers of patients have been apparently successfully treated with dicumarol. However, even when this technique is employed, the question remains whether slightly different methods yield comparable results. The purpose of the present study was to determine whether prothrombin concentration when calculated in this way is independent of the thromboplastin used in the test.

Methods. Studies were made on fresh plasmas obtained from human subjects and normal dogs, and from human patients and dogs receiving dicumarol. Blood was drawn into a dry syringe with care to prevent clotting or hemolysis and was immediately

mixed with 0.1 M sodium oxalate in the proportion of 9 to 1. The supernatant plasma was removed after centrifugation. Prothrombin-free plasmas were prepared by suspending barium sulfate powder or aluminum hydroxide cream in plasma, incubating at 37.5° C. for 10 minutes, and then removing the barium or aluminum salt by centrifugation. Prothrombin-free dog plasma was obtained by repeated administration of large doses of dicumarol to dogs until the plasma became incoagulable. The absence of prothrombin from these plasmas was demonstrated by the lack of clot formation on addition of thromboplastin and calcium.

Acetone-treated rabbit brain thromboplastin emulsion was prepared according to the method of Brambel.⁵ This preparation will henceforth be referred to as thromboplastin A. Two commercial tissue thromboplastins were used and were prepared in accordance with the instructions provided by the manufacturers. Bacto thromboplastin* will be referred to as thromboplastin B, and Maltine thromboplastin† as thromboplastin M. Russell viper venom (Stypven)‡ was employed as a 1 to 10,000 solution either in 0.5% phenol or in 0.85% sodium chloride.

All prothrombin time tests were performed according to a standard procedure. One-tenth cc. of the plasma to be tested was introduced into a 10 by 44 mm. test tube. One-tenth cc. of a thromboplastic preparation was added and the tube was placed in a water bath at 37.5° C. After several minutes 0.1 cc. of 0.025 M calcium chloride solution was blown into the tube and simultaneously a stop-watch was started. The prothrombin time was considered to be the interval between the addition of calcium chloride and the first indication of clot formation observed on tilting the tube. All determinations were made in duplicate.

Serial dilutions of normal plasmas were made and the prothrombin time of each dilution was determined with each thromboplastin. The diluents employed were 0.85% sodium chloride, oxalated saline prepared by mixing 9 parts of the sodium chloride solution with 1 part of 0.1 M sodium oxalate, and prothrombin-free plasmas prepared by the methods described above. In order to ensure absolute comparability of the results,

a sufficient quantity of each thromboplastin was prepared in one lot for an entire experiment. In each experiment a single normal plasma was used for making all of the dilutions. Curves were constructed showing the relationship between prothrombin concentration (*i. e.*, plasma dilution) and clotting time for each thromboplastin and for each diluent. Plasmas from patients receiving dicumarol were tested with portions of the same thromboplastic emulsions or solutions which had been used to establish these curves. By reference to the appropriate curve, the prothrombin content of the hypoprothrombic plasmas was estimated in terms of % of normal.

RESULTS. *Simultaneous Estimation of the Prothrombin Concentration of Human Hypoprothrombic Plasmas With 4 Thromboplastins, Using Saline as a Diluent.* A normal human plasma was serially diluted with 0.85% sodium chloride solution. From the clotting times obtained with each dilution, activity curves of the various thromboplastins were constructed. When these curves were compared, they were found to differ considerably from each other. The curves for thromboplastins A and M are shown in Figure 1. Thromboplastin A produced the greatest changes in clotting time for small changes in prothrombin concentration. Results obtained with thromboplastin M, on the other hand, showed the most asymptomatic relationship between clotting time and plasma dilution. After these curves had been established, the same thromboplastic preparations which had been employed to produce them were then immediately used to determine the prothrombin times of undiluted plasma from patients receiving dicumarol. With each clotting time obtained, reference was made to the appropriate activity curve and the result expressed in terms of % of normal prothrombin concentration. Table 1 combines the result of 5 experiments and shows some typical comparisons.

It is clear that when prothrombin con-

* Difco Laboratories, Detroit, Michigan.

† The Maltine Company, New York, New York.

‡ The Wellcome Physiological Research Laboratories, Beckenham, England.

centrations of hypoprothrombic plasma were estimated using thromboplastin M, the results usually indicated concentrations much lower than those obtained with the other thromboplastins. Stypten often gave values very much higher than the tissue extract thromboplastins. On some occasions clotting times obtained with Stypten were normal when results with other thromboplastins indicated severe prothrombin deficiency.

Comparison of Saline and Prothrombin-

free Plasmas as Diluents for Normal Dog Plasma. Experiments were performed on dogs to determine whether the discrepancy which had been observed between the results obtained with different thromboplastins could be explained by the use of saline as a diluent in constructing the reference curves. Fresh incoagulable blood from dogs treated with large doses of dicumarol was oxalated in the usual fashion. The plasmas obtained were used for preparing serial dilutions of

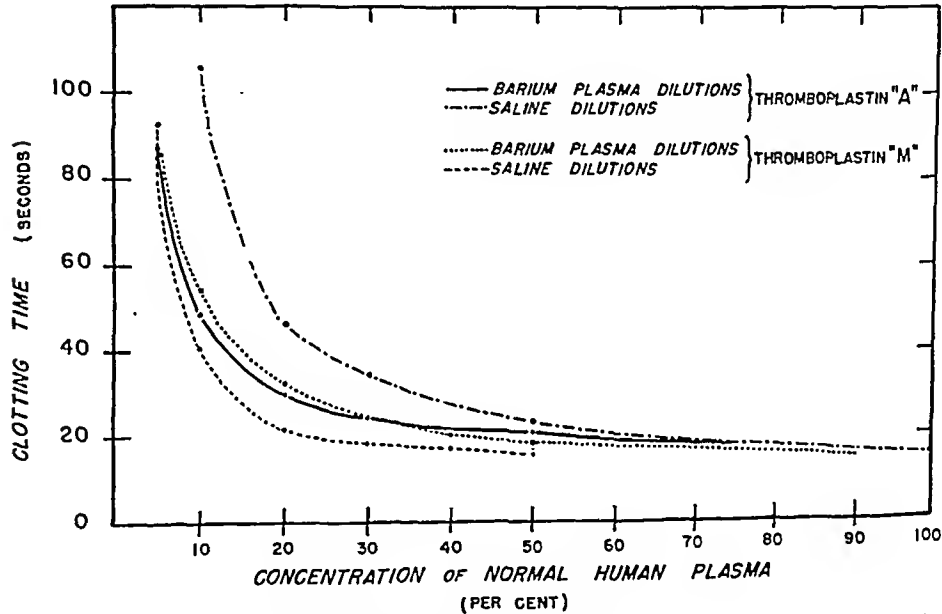


FIG. 1.—Clotting times of saline and barium plasma dilutions of a normal human plasma with thromboplastins A and M.

TABLE 1.—PROTHROMBIN CONCENTRATIONS OF PLASMAS OBTAINED FROM PATIENTS RECEIVING DICUMAROL, EXPRESSED AS % OF NORMAL AS DETERMINED BY 4 THROMBOPLASTINS USING SALINE DILUTION CURVES

Patient	Thromboplastin			
	A	B	M	Stypten
1	12	10	< 5	25
2	25	30	<10	50
3	25	25	10	40
4	25	..	<10	30
5	20	..	<10	30
6	20	18	<10	40
7	60	45	25	60
8	38	25	<10	36
9	32	..	18	
10	19	..	10	
11	50	..	35	
12	42	..	25	
13	20	..	10	
14	17	14	14	100
15	30	20	15	100

normal dog plasma. The clotting time of each dilution was determined with each thromboplastin. If dicumarol affects only prothrombin, it could be reasonably assumed that the only significant variable in these plasma dilutions was the prothrombin concentration. Parallel determinations were made at the same time using as diluents saline, oxalated saline, and dog plasma treated with barium sulfate and with aluminum hydroxide.

When dicumarolized (prothrombin-free) dog plasma was used as a diluent, a quite different clotting curve was obtained than when saline was used. When barium sulfate treated dog plasma was employed as a diluent, the results very closely approximated those obtained with dicumarolized dog plasma. On the other hand, when

the normal plasma was diluted with aluminum hydroxide treated plasma, the clotting times approximated those obtained with saline. Dog plasma diluted with oxalated saline gave essentially the same clotting times as when saline was used as a diluent. Figure 2 shows some of these results. With all of the thromboplastins tested, saline dilutions below about 15% gave clotting times which exceeded those obtained with corresponding dilutions with prothrombin-free plasma. This was probably a result of the reduced concentration of other plasma components including fibrinogen in the saline dilutions.⁶ The curves obtained with thromboplastin M are of interest in that saline dilutions of dog plasma above 15% gave slightly shorter clotting times than did

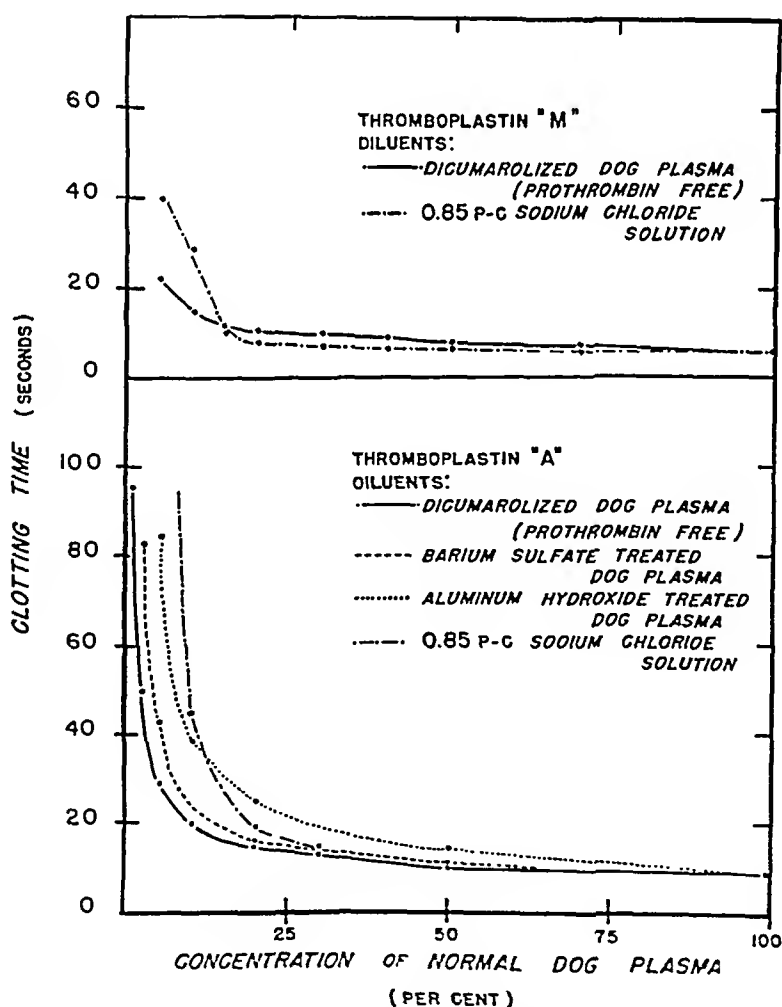


FIG. 2.—Two experiments showing clotting time concentration curves for dog plasma using several diluents and 2 thromboplastins.

the corresponding prothrombin-free plasma dilutions. On the other hand, with thromboplastins A and B the clotting times of saline dilutions tended to be longer than those of the corresponding dicumarolized dog plasma dilutions. Stypven caused oxalated dog plasma to clot without addition of calcium and therefore could not be studied.

Clot Accelerating Property of Normal Dog Plasma. The prothrombin times of normal dog plasma with all of the thromboplastins were much shorter than those of normal human plasma. The prothrombin activity curves were all more asymptotic than the corresponding curves for human plasma. The marked differences between the curves for the different thromboplastins which had been demonstrated for human blood were not seen

clotting time curve closely resembled the curve obtained with dilutions of normal dog plasma. The prothrombin times of plasmas from patients receiving dicumarol also were greatly shortened on addition of prothrombin-free dog plasma. Furthermore, oxalated prothrombin-free dog plasma, when added to oxalated hemophilic plasma, shortened the recalcification clotting time much more than did an equal quantity of oxalated normal human plasma. These clot accelerating effects were obtained after removal of the fibrinogen from the dog plasma by heating at 56° C. for 5 minutes but disappeared after heating at 65° C. for 5 minutes.

Prothrombin-free Human Plasma Used as a Diluent for Normal Human Plasma. Prothrombin activity curves for thromboplastin A were constructed using saline,

TABLE 2.—PROTHROMBIN CLOTTING TIMES, EXPRESSED IN SECONDS, OF SERIAL DILUTIONS OF A NORMAL HUMAN PLASMA, USING THROMBOPLASTIN A AND SEVERAL DILUENTS

2.—PROTHROMBIN CLOTTING TIMES, EXPRESSED IN SECONDS, FOR NORMAL HUMAN PLASMA, USING THROMBOPLASTIN A AND SEVERAL DILUENTS					Plasma from patient with hemorrhagic disease of newborn
Normal plasma (%)	0.85% sodium chloride	Diluent			
		Aluminum plasma (slow centrifugation)	Aluminum plasma (centrifuged at 5000 r.p.m.)	Barium plasma	
100	16	16	16	16	16
70	19	28	28	19	22
50	24	47	63	21	33
40	28	74	105	24	52
30	35	26	..
20	57	33	..
15	79	40	..
10	123	52	..
5	99	..

with dog blood. Only when the prothrombin concentration of dog plasma was reduced below about 25% was there any appreciable change in clotting time with any of the thromboplastins. This accelerated clotting of dog plasma is caused by a component of prothrombin-free plasma.¹⁰ When incoagulable plasma from a dicumarolized dog was added to normal human plasma, the prothrombin time of the mixture was shortened instead of being prolonged as it would have been by dilution with human prothrombin-free plasma. When serial dilutions of human plasma were made with prothrombin-free dog plasma, the prothrombin concentration-

barium plasma and aluminum hydroxide plasma as diluents for a normal human plasma. The relationship between these curves was similar to that observed in the dog (Table 2). Aluminum hydroxide plasma dilutions gave clotting times which were longer than the corresponding saline dilutions. As previously observed in the dog, aluminum plasma appeared to have a clot-retarding effect. After centrifuging the aluminum plasma at 5000 r.p.m. in an angle centrifuge for 10 minutes, it gave results approaching those obtained with saline. Apparently, as suggested by Tanturi and Banfi¹³ some of the aluminum hydroxide remained suspended after cen-

trifugation and absorbed a portion of the prothrombin of the plasma being diluted, thus prolonging the clotting time. With thromboplastin A the barium plasma dilutions always gave shorter clotting times than the corresponding saline or aluminum plasma dilutions.

A small amount of blood was obtained from an infant with hemorrhagic disease of the newborn. The prothrombin time of the plasma from this patient, determined with thromboplastin A, was 570 seconds. This virtually prothrombin-free plasma was used as a diluent for the normal plasma being tested. The clotting times of the normal plasma so diluted were found to be identical with the clotting times of the same normal plasma correspondingly diluted with barium plasma (Table 2). Barium sulfate-treated plasma thus appeared to be a suitable prothrombin-free plasma for use as a diluent. Provided that enough barium sulfate was used to remove all of the prothrombin, variations in the quantity of barium sulfate employed had no demonstrable effect.

thromboplastins A, B and M. Results are shown in Table 3 (see also Fig. 1). The curves for thromboplastins A and M were almost superimposable when barium plasma was employed as a diluent. When saline was used, however, the clotting times of the various dilutions were relatively prolonged for thromboplastin A and relatively shortened for thromboplastin M. Saline dilution thus affected the action of these 2 thromboplastins in exactly opposite ways. This suggests that there are components of plasma other than prothrombin which accelerate the clotting action of thromboplastin A and which inhibit thromboplastin M. These observations were confirmed in 5 separate experiments using several different lots of the thromboplastins and several normal plasmas.

Prothrombin times of plasmas from patients receiving dicumarol were then determined with each thromboplastin and the prothrombin concentrations calculated in terms of % of the normal. As in previous experiments, portions of the same thromboplastic preparations which had

TABLE 3.—PROTHROMBIN CLOTTING TIMES, EXPRESSED IN SECONDS, OF SERIAL DILUTIONS OF A NORMAL HUMAN PLASMA USING 0.85% SODIUM CHLORIDE AND BARIUM SULFATE TREATED PLASMA AS DILUENTS*

		Concentration of normal plasma (%)							
Thromboplastin	Diluent	100	50	40	30	20	10	5	2.5
A	Saline		24	..	35	47	108		
	Barium plasma	16	21	..	25	30	49	88	
B	Saline		20	23	25	28	66	>200	
	Barium plasma	14	17	18	21	25	38	54	120
M	Saline		16	18	19	22	41	94	
	Barium plasma	14	19	21	25	33	55	87	167

* Three thromboplastins, A, B and M were employed.

Simultaneous Estimation of the Prothrombin Concentration of Human Hypoprothrombic Plasmas with 3 Thromboplastins, Using Prothrombin-free Plasma as a Diluent. Clotting time-prothrombin concentration curves of a single normal human plasma using saline and barium plasma as diluents were prepared for

been used to establish the clotting time-concentration curves were employed to test the hypoprothrombic plasmas. The calculated prothrombin percentages of the hypoprothrombic plasmas when determined with thromboplastin A or B were lower when barium plasma was used as a diluent in constructing the reference

curves than when saline was used. With thromboplastin M the converse was true. The prothrombin concentrations calculated from the barium plasma curves for the different thromboplastins showed close agreement in only about 50% of the plasmas studied. In the remainder, thromboplastin M now gave results distinctly higher than those obtained with thromboplastin A, a difference which was opposite in direction to that observed when saline dilutions were used (Table 4).

prepared from the blood of a patient who was receiving dicumarol had a definite clot retarding effect and behaved as if it contained an anticoagulant (Table 5, Patient 10). However, barium plasmas from 9 other dicumarolized patients, some of whom had more severe degrees of hypoprothrombinemia, gave essentially the same results as barium treated normal plasma. Thus no evidence was obtained that dicumarol significantly affected any plasma component other than prothrom-

TABLE 4.—PROTHROMBIN CONCENTRATIONS OF PLASMAS OBTAINED FROM PATIENTS RECEIVING DICUMAROL, ESTIMATED FROM BARIUM PLASMA AND SALINE DILUTION CURVES*

Patient	Thromboplastin	Plasma prothrombin concentration (% of normal)	
		Estimated from barium plasma dilution curve	Estimated from saline dilution curve
1	A	9	17
	M	23	14
	B	8	14
2	A	17	30
	M	25	15
	B	17	20
3	A	8	16
	M	21	16
4	A	13	23
	M	12	8
5	A	12	20
	M	14	9
6	A	10	23
	M	22	18
7	A	22	38
	M	24	20
8	A	12	25
	M	17	13
9	A	25	41
	M	24	20
10	A	22	38
	M	24	20

* Thromboplastins A, B and M were used.

Prothrombin-free Plasmas From Different Human Sources Used as Diluents for a Normal Plasma. Barium plasma was prepared from the blood of normal individuals, patients receiving dicumarol and a small group of patients with various diseases. When these barium plasma were used concurrently as diluents for the same normal plasma, superimposable clotting time curves were generally obtained (Table 5). In 1 instance barium plasma

bin. In 2 experiments barium plasma was prepared from the blood of the dicumarolized patients being studied, and these barium plasmas were used as diluents for a normal plasma to construct the activity curves for thromboplastins A and M. Even when this was done, determinations with thromboplastin M yielded prothrombin concentrations approximately twice as high as with thromboplastin A for these 2 patients.

Effect of Changes in Concentration on the Activity of a Thromboplastin. Having demonstrated the lack of comparability of different thromboplastins we next studied the alterations in behavior of a single thromboplastin resulting from changes in its concentration. Only thromboplastin A was included in this experiment. A standard thromboplastic emulsion A was serially diluted with saline and each of

the diluted preparations was employed to determine the prothrombin time of the following: normal plasma, the same normal plasma diluted to 20% with saline, normal plasma diluted to 20% with barium plasma, and undiluted plasma from 2 patients receiving dicumarol. The results are shown in Figure 3. Dilution of the thromboplastin to as low as 25% of its original concentration had a very slight

TABLE 5.—CLOTING TIMES IN SECONDS OF 20% AND 10% DILUTIONS OF NORMAL HUMAN PLASMA, USING AS DILUENTS BARIUM SULFATE TREATED PLASMAS FROM 10 PATIENTS, 8 OF WHOM WERE RECEIVING DICUMAROL

Exp.	Thromboplastin	Source of barium plasma	Concentration of normal human plasma		
			100%	20%	10%
Exp. 1	A	Normal subject	16	36	58
		Patient 1 (dicumarol)		39	
		Patient 2 (dicumarol)		37	
		Patient 3 (dicumarol)		43	
		Patient 4 (dicumarol)		43	
		Patient 5 (dicumarol)		39	
		Patient 6 (dicumarol)		39	
Exp. 2	A	Normal subject	19	40	61
		Patient 7 (postoperative laparotomy)		39	66
		Patient 8 (hyperglobulinemia)		42	64
Exp. 3	A	Normal subject	17	34	54
		Patient 9 (dicumarol)		37	66
		Patient 10 (dicumarol)		63	114
Exp. 4	M	Normal subject		29	44
		Patient 9 (dicumarol)	16	28	42
		Patient 10 (dicumarol)		68	97

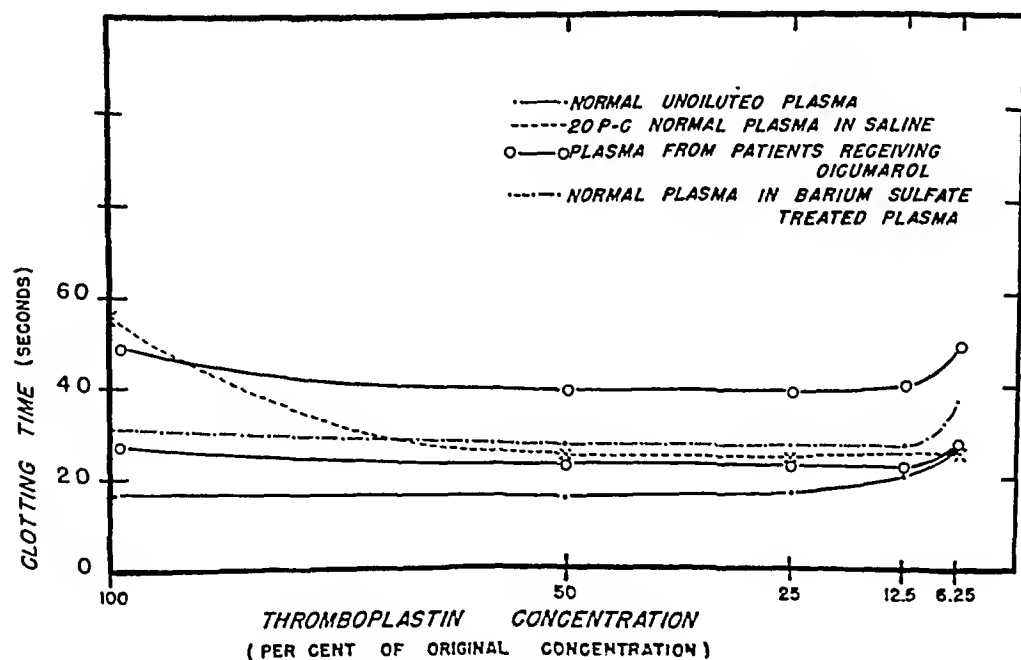


FIG. 3.—Effect of altering the concentration of thromboplastin A on the clotting times obtained with normal, hypoprothrombic and diluted plasmas.

clot-accelerating effect on all of the plasmas tested except the one diluted with saline, which showed marked shortening of the clotting time. With further dilution of the thromboplastin below 25% the clotting times of all of the plasmas became increasingly prolonged. The 20% plasma in saline gave a longer clotting time than any of the other plasmas being tested when the standard undiluted thromboplastin A was used; but with a 6.25% thromboplastin, it gave a clotting time shorter than those of the other plasmas. Thus thromboplastin A, when diluted to 6.25% gave results which resembled those previously obtained with thromboplastin M, *i. e.*, plasma diluted with saline gave a shorter clotting time than when equally diluted with barium plasma. As a matter of fact, in this particular case 20% normal plasma in saline gave about the same clotting time as the normal undiluted plasma.

Discussion. The necessity for standardization of the prothrombin test has been emphasized in clinics where dicumarol is being used.^{4,5} Allen³ has recently called attention to the need for expression of the results of prothrombin tests in terms which will make comparison of the results of different investigators possible. It has apparently been generally assumed that if results of the tests are expressed in terms of % of normal prothrombin determined by reference to clotting time-dilution curves of normal plasma, such comparability can be achieved. Our studies show that this is not true. When the prothrombin concentration of plasma from a patient receiving dicumarol is estimated by methods which are identical except for variations in the nature or quantity of thromboplastic substance used, grossly different results may be obtained. One thromboplastin may regularly give apparent prothrombin concentrations lower than those obtained with another thromboplastin.

The studies which have been presented shed some light on the cause of this discrepancy. The reaction of thromboplastin

with prothrombin is apparently very complex, and both plasma and thromboplastic preparations appear to contain clotting accelerators and inhibitors whose interaction, as well as the prothrombin concentration, affect the result of the test. The presence of unknown factors in plasma which may influence the rate of clotting has been suggested by other investigators.⁶ In our experiments the action of thromboplastin A was found to be enhanced by prothrombin-free plasma, so that when such plasma was used to dilute normal plasma, shorter clotting times were obtained than when saline was used as a diluent. On the other hand, thromboplastin M appeared to be inhibited by prothrombin-free plasma, and the use of saline as a diluent gave shorter clotting times. On the basis of these results it is apparent why prothrombin concentrations calculated from saline dilution curves are regularly higher for thromboplastin A than for thromboplastin M.

This discrepancy theoretically should be overcome if an ideal prothrombin-free plasma could be used as a diluent in constructing the activity curves. Such a diluent should be identical with the plasma being tested except for lack of prothrombin. In an attempt to obtain such a diluent we have used plasma from which the prothrombin has been removed by treatment with barium sulfate and aluminum hydroxide, plasma from dogs rendered prothrombin-free with dicumarol, and plasma from an infant with hemorrhagic disease of the newborn. Comparison of the results obtained with these plasmas show that in dogs, barium sulfate-treated plasma closely resembles the plasma obtained after administration of sufficient dicumarol to render the blood incoagulable. Human barium plasma could not be distinguished from the plasma obtained from a severely prothrombin deficient infant. Aluminum hydroxide-treated plasma, on the other hand, is not comparable to the prothrombin-free plasmas prepared in other ways and seems to have a slight clot-retarding action.

On estimating the prothrombin concentration of a hypoprothrombic plasma using several thromboplastins and their appropriate barium plasma reference curves, a discrepancy between the results obtained frequently persisted. This observation suggests that (1) barium plasma differs in an obscure way from an ideal prothrombin-free plasma, (2) dicumarol alters prothrombin qualitatively so that it responds differently to different thromboplastins, or (3) dicumarol alters some other plasma component which affects various thromboplastins differently.

We were unable to demonstrate a significant difference between plasmas treated with barium sulfate and plasmas lacking prothrombin as a result of physiologic disturbance. We have not shown that the prothrombin which remains in the blood after administration of dicumarol is altered in any way, but this remains a theoretical possibility. Finally, on comparing barium plasma obtained from a number of sources including the blood of dicumarolized patients, we were unable to demonstrate any difference between the prothrombin-free plasmas of patients receiving dicumarol and the plasmas of normal individuals similarly treated. We did find definite evidence of the presence of an anticoagulant in the barium plasma from 1 patient, but the nature of the clot-retarding component of this plasma was not determined. We feel that this isolated finding is sufficiently stimulating to warrant a systematic study of barium plasmas from patients with various diseases to determine their effects on the clotting time of normal plasma. It is possible that alterations in clot-inhibiting and clot-accelerating mechanisms might be demonstrated in that way. It would be of great interest to study barium plasmas from patients predisposed to thrombosis to determine whether a clot-accelerating property can be demonstrated. It is possible that the "hyperprothrombinemia" reported by some investigators¹² in such cases might be shown to be the result of the

presence of a clot-accelerator in prothrombin-free plasma.

There is no doubt that prothrombin-free plasma may contain substances apart from fibrinogen which have important effect on the rate of clotting. The accelerated clotting of dog plasma as compared with human plasma is caused by such a factor. This clotting accelerator in prothrombin- and fibrinogen-free dog plasma was found to withstand heat at 56° C. for 5 minutes and to be destroyed at 65° C. It had an amazingly potent clot accelerating action on normal, hypoprothrombic and hemophilic human plasma. The nature of this factor is unknown. It has been considered by Quick¹⁰ to be "prothrombin A" but it seems unlikely to us that it should be classified with prothrombin at all. Further studies are in progress to determine its nature. Probably a similar substance is present in human plasma in lower concentration. The relatively prolonged clotting times of high saline dilutions of plasma as compared with prothrombin-free plasma dilutions, are probably due to lack of this factor as well as to the decreased fibrinogen concentration.

Our studies clearly show that results obtained with different thromboplastins are influenced in different ways by factors other than prothrombin. Stypven in particular seems to be subject to influence by other plasma components. The work of Rapoport¹¹ suggests that plasma components other than prothrombin affect clotting times obtained with Stypven. We have repeatedly found that some plasmas which appear to be severely hypoprothrombic when tested with tissue thromboplastins give normal clotting times with Stypven. This may occur whether the prothrombin-deficient plasmas are obtained from patients with jaundice or from patients receiving dicumarol. Stypven gave results which were not consistently related to the results obtained with tissue thromboplastins. For these reasons we consider Stypven to be an unsatisfactory thromboplastin for use in the prothrombin

test. If used to control dieumarol therapy, it apparently could be dangerous.

The tissue extract preparations which were studied, when prepared in a standard way, gave results which while not at all comparable, at least showed consistent differences. It is not known how much these differences depend on qualitative and how much on quantitative variations in the thromboplastins. However, when merely the concentration of a single thromboplastin was altered, divergent results were obtained. This can be explained only by assuming that the thromboplastin contained both clotting accelerator and clotting inhibitor factors which were differentially affected by dilution. In thromboplastin A the clotting inhibitor was rendered less effective when the thromboplastin was diluted, so that clotting times obtained with the diluted thromboplastin were shorter than those with the original preparation. This clotting inhibitor in thromboplastin A was opposed by some component of plasma, so that when clotting times of whole plasma were determined, the times were shorter than when saline dilutions of plasma were used, even though the prothrombin concentrations were the same in both instances. After dilution of the thromboplastin, this prolongation of the clotting time of saline-diluted plasma no longer occurred. Thus the difference between the clotting times of a plasma equally diluted with prothrombin-free plasma and with saline may be in part the result of an effect on the thromboplastin itself of the difference in plasma concentration.

It is apparent that the results of prothrombin tests performed in one laboratory cannot be compared to results obtained elsewhere. Even when thromboplastin from the same source is used, the results may not be comparable. When different thromboplastins are employed, comparison of results is difficult if not impossible. The order of magnitude of the discrepancies between different methods is not small.

Caution should be used in interpreting the results of a test which is subject to

the influence of so many variables. Alterations in the prothrombin time do not necessarily imply changes in prothrombin concentration. In assessing the effects of drugs and other agents on the prothrombin concentration, the possibility that something other than change in prothrombin is causing the change in clotting time should always be borne in mind. Refinements of the prothrombin test designed to increase its sensitivity, such as the use of saline dilutions of plasmas being tested, must be regarded with some skepticism. When plasma is mixed with saline, much more than simple dilution of prothrombin occurs. Accurate interpretation of results so obtained requires more knowledge than we have at the present time.

Summary. The prothrombin concentrations of hypoprothrombic plasmas were determined, using a standard adaptation of Quick's method and 4 different thromboplastic preparations. When these prothrombin concentrations were estimated by reference to saline dilution-clotting time curves of normal plasma, markedly different results were obtained with the different thromboplastins. When prothrombin-free plasma was used as a diluent instead of saline, agreement between the results obtained with some of the thromboplastins was improved, but it was not possible to obtain strict comparability. Evidence was obtained that normal plasma contains factors other than prothrombin which affect different thromboplastins in different ways. Prothrombin-free plasma contains factors other than fibrinogen which may have an important effect on the rate of clotting. Thromboplastic preparations themselves may contain both clot-accelerating and clot-inhibiting components. The exceedingly complex nature of the interaction between thromboplastin and plasma was demonstrated.

At present it appears to be difficult if not impossible to compare prothrombin levels reported from one laboratory with those obtained in another. Unless steps are taken to make the results of prothrombin tests more comparable, some of the

value of the extensive clinical studies of dicumarol now being conducted will be lost. A thromboplastin should be selected which is least affected by variations in plasma components other than prothrombin. The use of prothrombin-free plasma as a diluent in constructing reference curves is an essential step toward achieving comparability. Under the best of circumstances, results obtained with different prothrombin methods apparently cannot be made to give perfect agreement.

We wish to express our gratitude to Dr. Beverly H. White, Department of Surgery, who provided all of the dog plasma used in our experiments, and to Dr. Charles E. Brambel, Mercy Hospital, Baltimore, Maryland, who demonstrated to us the technique of preparation of his thromboplastic reagent.

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STUDY OF FIXED TISSUE SECTIONS OF STERNAL BONE MARROW OBTAINED BY NEEDLE ASPIRATION

I. METHOD AND THE MORPHOLOGY IN VARIOUS CONDITIONS

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STUDY of the sternal bone marrow has proven to be of value as a diagnostic procedure in many conditions. Most observers have relied upon the cytology of smears, the nucleated cell count and the volumetric pattern in estimating the activity of the marrow.^{5,7,8,9} Although these studies furnish valuable information they offer only indirect evidence of the functional state of the marrow, the histologic structure and the relationship of the cells *in situ*. Errors in determining the absolute number of bone marrow elements may occur due to dilution of the marrow with peripheral blood and the relative numbers of each cell type cannot always be assayed with certainty from smears alone. The importance of studying fixed tissue sections for accurate evaluation of the bone marrow activity has, therefore, been emphasized repeatedly.^{3,4}

Many methods have been devised to study the histopathology of the bone marrow clinically. Surgical trephine has been used to obtain material for tissue sections,^{3,4} but this method is not as simple as needle aspiration biopsy and is, therefore, not as desirable for routine use. Material for other methods of estimating the activity of the marrow, such as the nucleated cell count and volumetric pattern, are likewise not obtained by this method.

Because of the ease and simplicity of sternal puncture, preparation of histologic sections from aspirated material would be preferable if the results obtained were as

reliable. Amprino and Penati,¹ and Merzans⁶ obtained tissue section of the marrow by allowing the aspirated material to clot. The coagulum was then fixed, embedded in celloidin and sectioned. By this method, however, the volumetric pattern and nucleated cell count are not obtained and the marrow particles remain dispersed in the blood so that adequate sampling may be difficult. Schleicher and Tucker^{9,10} described a method for fixing, embedding and sectioning serially the individual gross marrow particles that are present in the aspirated marrow and have repeatedly demonstrated the value of histologic section in a wide variety of diseases. This method requires special techniques and appears to us to be too difficult and time-consuming for ordinary routine use. Recently, Berman and Axelrod² described a method of obtaining smears, volumetric readings, imprints and histopathologic sections from 1.5 cc. of aspirated material. In this method the individual marrow particles adhering to the sides of a paraffin vial and the syringe are carefully collected, placed on a thrombin-coated area of a glass slide and clotted with plasma. The coagulum is then fixed, embedded and sectioned. It has been our experience, however, that difficulty is sometimes encountered in transferring these minute particles, and many may be lost by adhering to the sides of the vial or to the implements used in transfer. Some are crushed and some are too small to collect, so that when the yield in marrow particles

is poor, a satisfactory preparation cannot be obtained.

This paper describes a method for obtaining histologic sections of the bone marrow from aspirated material adapted to routine use and avoids manipulation of individual particles. Smears, imprints, nucleated cell counts and the volumetric pattern are also obtainable for comparison by this method.

Method. Routine aseptic precautions and local anesthesia with procaine are used. The sternal puncture needle is an ordinary lumbar puncture needle with stylet cut down so that the shaft of the needle is 4 to 5 cm. in length and has a shallow bevel. The body of the sternum at the level of the second interspace is entered by the usual technique. The manubrium and other portions of the body of the sternum are also satisfactory sites. The first small drop of marrow obtained is expelled upon a glass slide and is used to make several smears. One cc. of material is then aspirated and is placed in a bottle containing 0.2 cc. of Wintrobe anticoagulant* which has been evaporated to dryness.

A nucleated cell count is made and the aspirated material is then transferred to a hematocrit tube. The tube is centrifuged at 2500 revolutions per minute for 20 minutes to obtain the volumetric pattern which consists of the myeloid-erythroid layer, fat, red blood corpuscle and plasma content.

After the blood has been removed from the bottle containing anticoagulant, gross marrow particles are almost invariably seen adhering to the sides. These particles are washed down with plasma. The suspension of gross marrow particles in plasma is then transferred to a small test tube (10 by 1.5 cm.) with the pipette designed for use with the Wintrobe hematocrit tube and is allowed to sediment for 10 to 30 minutes in an ice-box at about 4° C. This allows the marrow particles to aggregate, usually on the top but occasionally on the bottom, depending upon the specific gravity of the individual particles. The surplus plasma is carefully aspirated with a Wintrobe pipette, care being taken not to remove any particles. The smallest amount of plasma possible to

suspend the particles is allowed to remain, assuring a high concentration of marrow in the final preparation. One drop of 0.25 M calcium chloride is added to clot the plasma. Excess calcium prevents formation of the clot and rarely a drop of thromboplastin solution may be necessary to insure clotting. The resultant clot containing the marrow particles is placed in Zenker's acetic fixative for 30 minutes to 1 hour, and rinsed briefly in tap water. The material is then placed in 50% alcohol and is dehydrated through 60, 70, 85, 95% and absolute alcohol and xylene. The tissue is allowed to remain in each alcohol solution for about 1 hour and in the xylene for about 45 minutes. It may be allowed to remain overnight in the 85% alcohol. Three changes are made within each hour beginning with 95% alcohol. It is then infiltrated with paraffin containing about 2% beeswax, 3 changes of this paraffin mixture being employed within a period of 2½ to 3 hours. It is then embedded, sectioned serially at 4 μ and stained with Harris' hematoxylin and eosin.

Discussion. With this method histologic sections of the bone marrow, as well as smears, nucleated cell count and volumetric pattern can be obtained almost routinely. Those specimens yielding many large particles are easiest to prepare, but occasionally only a few particles can be seen adhering to the glass vial. In these cases it is more difficult and occasionally impossible to gather enough material to make a tissue block. The failures are infrequent, occurring chiefly with hypoplastic or sclerotic bone marrow. With increasing experience practically all of the specimens yield material satisfactorily for section.

The histologic appearance of the marrow is comparable to that obtained by trephine and does not appear to be distorted. Bone spicules, small arterioles and capillaries are frequently present. The normal relationship of cells, sinusoids and fat is intact. Correlation of the appearance of antemortem sections with postmortem sections is excellent.

* Wintrobe anticoagulant contains 1.2 gm. of ammonium oxalate and 0.8 gm. of potassium oxalate per 100 cc. of distilled water. With 0.2 cc. of this anticoagulant the total final salt concentration is 2 to 3 mg. per cc. of blood.

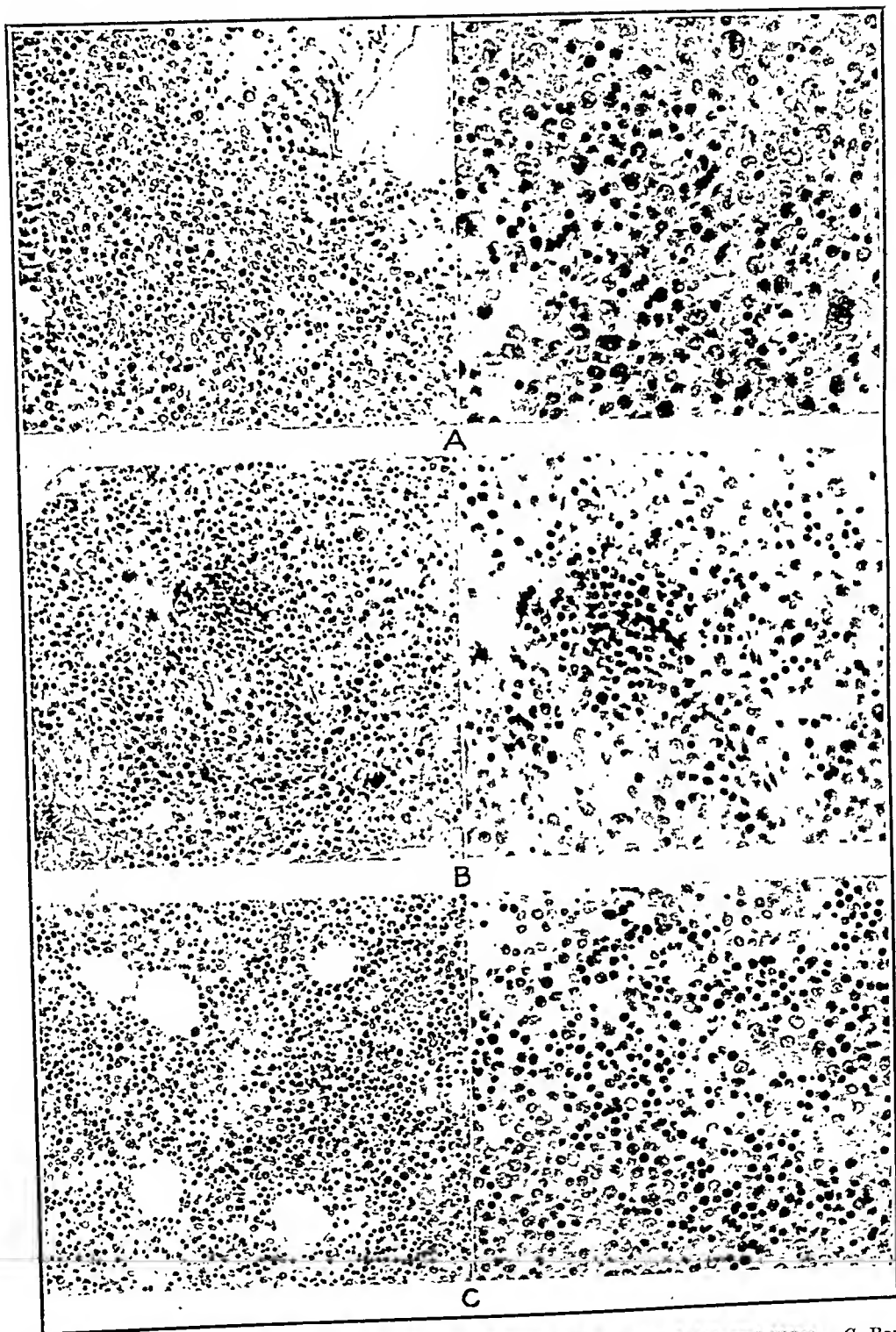


FIG. 1.—A, Normal marrow 155X and 300X. B, Hypoplastic marrow 155X and 300X. C, Bone marrow in polycythemia vera 155X and 300X.



FIG. 2.—A, Bone marrow in pernicious anemia in relapse 155X and 300X. B, Bone marrow in pernicious anemia during therapy 155X and 300X. C, Bone marrow in chronic hemolytic anemia 155X and 300X.

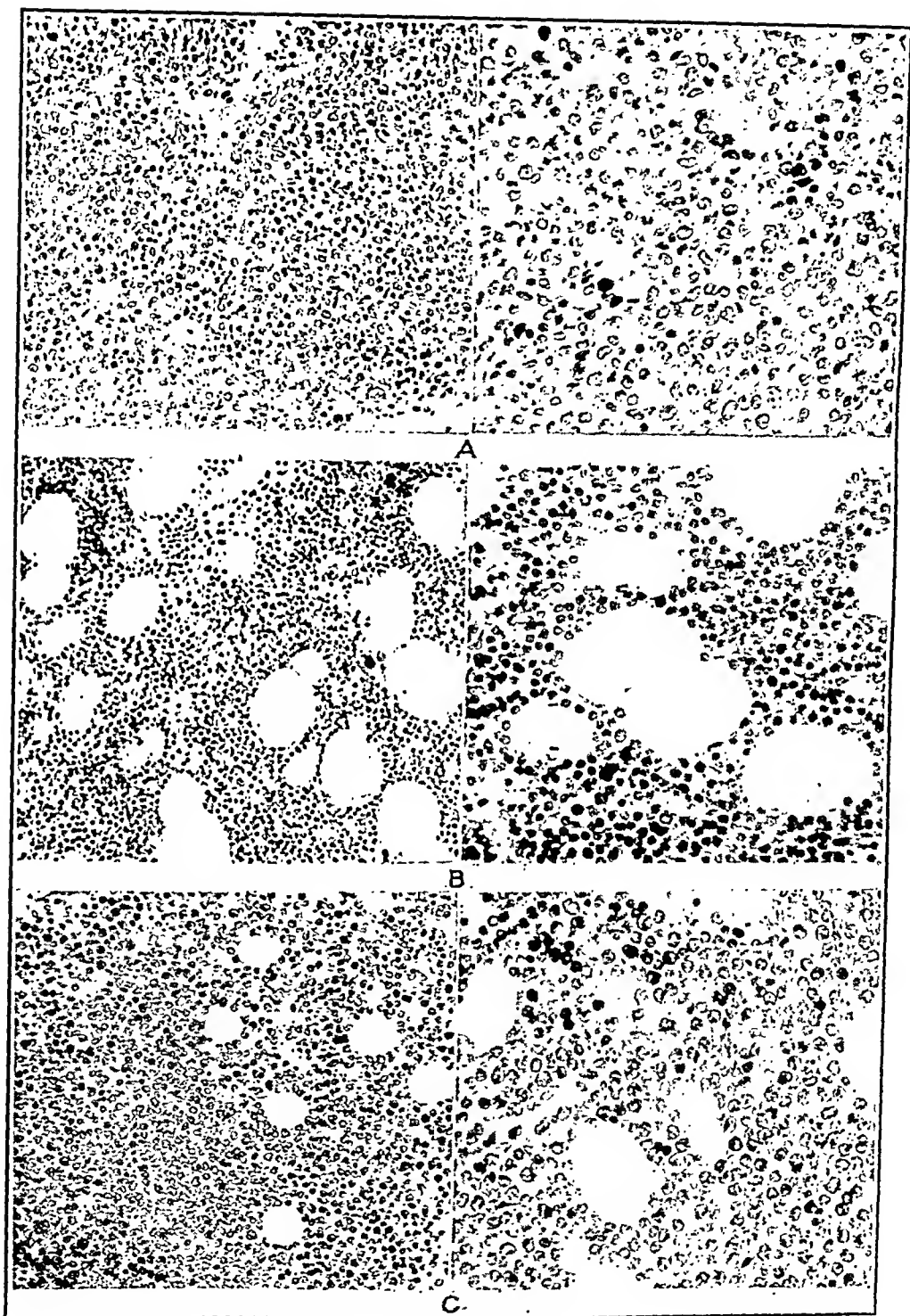


FIG. 3.—A, Bone marrow in chronic myeloid leukemia 155 \times and 300 \times . B, Bone marrow in chronic lymphatic leukemia 155 \times and 300 \times . C, Bone marrow in acute myeloid leukemia 155 \times and 300 \times .

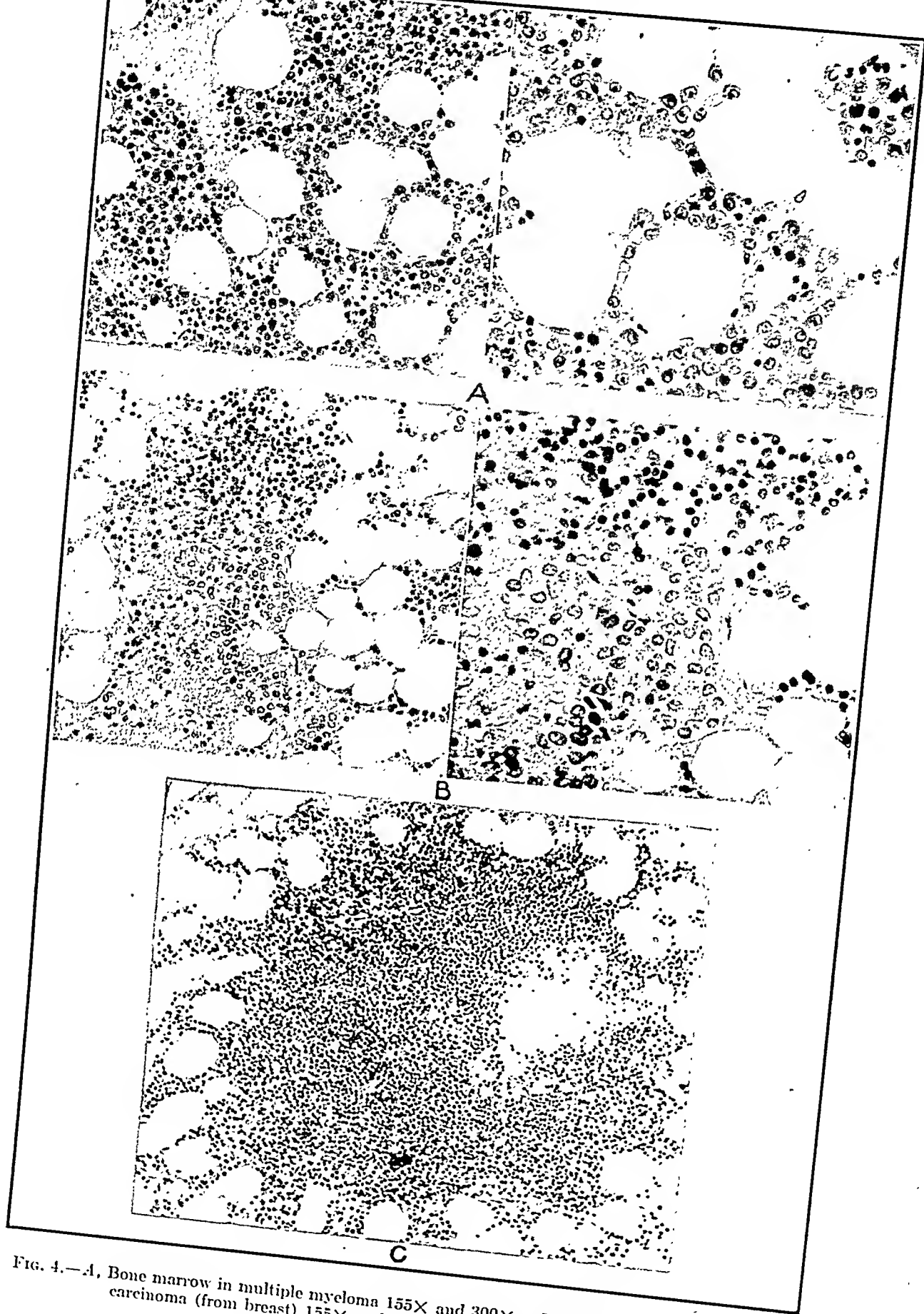


FIG. 4.—A, Bone marrow in multiple myeloma 155X and 300X. B, Bone marrow with metastatic carcinoma (from breast) 155X and 300X. C, Solitary lymph follicle 70X.

Representative portions from some of the more typical sections have been included in the accompanying photomicrographs. The typical architecture and the distribution of cells and fat in a normally active marrow (Fig. 1, *A*) is shown in contrast to the relatively fatty, acellular marrow of hypoplastic anemia (Fig. 1, *B*). In polycythemia vera (Fig. 1, *C*) the complete replacement of the normal architecture by an overabundance of cells of the granulocytic and erythroid series, the absence of fat cells and the marked increase in the numbers of megakaryocytes are characteristic. In pernicious anemia in relapse, the increased cellularity of the bone marrow, the absence of fat cells and the large numbers of megaloblasts are typical (Fig. 2, *A*). The appearance of islands of erythroblastic maturation during therapy is readily seen (Fig. 2, *B*). The active marrow encountered with the chronic hemolytic anemia shows marked erythroblastic hyperplasia (Fig. 2, *C*). In chronic lymphatic leukemia, the normal architecture persists in the case shown, but the infiltration with lymphocytes is quite evident (Fig. 3, *B*). In chronic myeloid leukemia, however, the normal marrow is entirely replaced by large numbers of cells of the myeloid series and there is an absence of fat cells (Fig. 3, *A*). The replacement of the normal marrow by large numbers of blast cells in acute myeloid leukemia is shown in Figure 3, *C*.

The infiltration of plasma cells in the marrow with persistence of the normal architecture in a case of multiple myeloma is seen in Figure 4, *A*. Solitary lymph follicles (Fig. 4, *C*) were not uncommon and occurred in marrows of aplastic anemia, generalized tuberculosis, carcinoma and debility. In 1 instance a nodule of monocytes was found.

A syncytium of metastatic tumor cells was found not infrequently in patients with malignancy (Fig. 4, *B*), especially in cases of carcinoma of the breast, bronchus or prostate. No patients with carcinoma of the thyroid or kidney were examined, but it is not unlikely that metastases to the sternal marrow could be detected in many of these cases. Metastatic carcinoma was found in the sternal marrow in 1 case when all the other studies, including extensive Roentgen ray examinations, failed to reveal a suspected malignancy. More extensive study is necessary to determine the incidence of metastases to the sternal marrow and the value of this procedure in diagnosis and prognosis.

Summary. A method of obtaining histologic sections of the sternal bone marrow from aspirated material is described. Histologic sections can be obtained routinely along with smears, nucleated cell count and volumetric pattern by this method. Some typical histopathologic findings are presented.

We wish to acknowledge the aid and suggestions of Dr. H. T. Karsner and Dr. H. Z. Lund of the Institute of Pathology in preparing the photomicrographs.

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STUDY OF FIXED TISSUE SECTIONS OF STERNAL BONE MARROW OBTAINED BY NEEDLE ASPIRATION

II. COMPARISON OF NUCLEATED CELL COUNT AND VOLUMETRIC PATTERN WITH HISTOLOGIC APPEARANCE

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QUANTITATIVE estimation of the activity of the bone marrow from the nucleated cell count² and the volumetric pattern^{1,4} is often unreliable. Many errors are possible with this technique so that there is considerable doubt as to whether this method furnishes a reliable index as to the functional state of the bone marrow. It is therefore essential to compare the nucleated cell count, the myeloid-erythroid volume and the fat content with the histologic appearance of the marrow in a wide range of conditions.

Material and Methods. The histologic appearance of the sternal bone marrow was compared with the values for the nucleated cell count, myeloid-erythroid volume and fat content in 60 patients. The material for histologic section, the nucleated cell count and the volumetric pattern were all obtained from the same sample of aspirated marrow by the technique described in the preceding paper.

With a 5 cc. syringe, 1 cc. of material was aspirated in each case. Small errors of dilution were, of course, unavoidable. The nucleated cell count, the myeloid-erythroid volume and the fat content were determined from this aspirated marrow and the histologic sections were then prepared from the gross marrow particles remaining. The activity of the marrow was estimated from the histologic sections. Inspection of many serial sections was necessary for an accurate estimate because of the variations in cellular and fat content of different portions of the sternal marrow. Estimations as to the cellularity of the marrow were arrived at inde-

pendently by the authors with remarkable agreement and with no essential difference of opinion. The marrows were arbitrarily classified as hypoplastic, normal, moderately hyperplastic and hyperplastic depending upon the cellular density. The fat content of the histologic sections was also estimated by inspection and was classified as normal, reduced or increased in quantity.

RESULTS. The results are summarized in the accompanying tables. Twenty-nine cases were classified as having normal cellularity after study of fixed tissue sections (Table 1) and in these the nucleated cell count ranged from 6300 to 247,000 cells per c.mm., with an average of 58,250 cells per c.mm. The myeloid-erythroid volumes ranged from 1 to 17 %, with an average of 5 %, and the fat content ranged from 0.25 to 8 %, with an average of 1.7 %. The fat content in the histologic sections was judged to be increased in only 4 of these cases and normal in the remainder.

Thirteen cases were classified as being hypoplastic (Table 2). The nucleated cell count ranged from 5000 to 59,250 cells per c.mm., with an average of 22,615. The myeloid-erythroid volume ranged from 0.5 to 5.5 %, with an average of 2.1 %, and the fat content ranged from zero to 3 %, with an average of 1.4 %. Histologically, the fat content was normal in 3 cases, increased in 9 cases and decreased in only 1 case. In the latter case (Case 47) the marrow was replaced to a large extent by metastatic carcinoma.

Ten cases were classified as showing moderate hyperplasia on histologic section (Table 3). In these cases the nucleated cell count ranged from 29,250 to 850,000 cells per c.mm., with an average of 142,175 cells per c.mm. The myeloid-erythroid volume ranged from 3.5 to 40%, with an average of 8.65%, and the fat content ranged from zero to 4.5%, with an average of 1%. In the histologic sections the fat content was decreased in 6 and normal in 4 of the cases.

was good in the majority of cases. The mean values for the nucleated cell count and myeloid-erythroid volume in those cases with a normal histologic pattern fell within the range of normal values established by others.^{1,2} The mean values in the hypoplastic and hyperplastic marrows varied in the expected direction.

The correlation between the nucleated cell counts, and myeloid-erythroid volume was best in those cases showing hypoplasia histologically and poorest in those showing

TABLE 1.—CASES SHOWING NORMAL ACTIVITY HISTOLOGICALLY

Case No.	Volumetric pattern			Histologic pattern		Clinical diagnosis
	Nucleated cell count	Myeloid-erythroid layer	Fat content	Cellularity	Fat content	
2	37,500	3.5	1.0	Normal	Normal	Fever of unknown etiology
3	68,000	4.0	1.0	Normal	Normal	Carcinoma of breast, no metastases
4	52,500	4.0	1.0	Normal	Normal	Polycythemia vera (treated)
5	43,750	4.0	1.5	Normal	Normal	Atypical monocytic leukemia
7	64,750	6.0	0.5	Normal	Normal	Splenic neutropenia
8	247,000	13.0	1.5	Normal	Normal	Idiopathic thrombocytopenic purpura
9	16,250	1.0	1.0	Normal	Normal	Multiple sclerosis
11	132,000	17.0	8.0	Normal	Increased	Severe pulmonary emphysema (moribund)
12	160,250	14.0	1.0	Normal or sl. hyperplastic	Normal	Mycosis fungoides
13	76,750	7.0	1.0	Normal	Increased	Scleroderma
22	6,300	1.0	1.0	Normal	Normal	Carcinoma of the stomach
26	39,500	2.25	0.25	Normal	Normal	Hypochromic anemia cause undetermined
30	51,000	3.5	1.0	Normal	Normal	Pneumonia, pneumococcal
31	79,250	5.0	3.5	Normal	Normal	Pernicious anemia, treated
35	25,000	4.0	0.5	Normal	Normal	Pulmonary tuberculosis
37	67,500	5.0	0.25	Normal	Normal	Pulmonary fibrosis with secondary polycythemia
38	10,000	1.5	0.5	Normal	Normal	Mediastinal tumor
39	21,000	1.0	1.0	Normal	Increased	Carcinoma of breast (male)
41	63,500	8.0	4.0	Normal	Normal	Carcinoma of breast, no metastases
42	87,000	3.0	2.5	Normal	Normal	Carcinoma of breast, no metastases
48	74,250	4.5	2.0	Normal	Increased	Normochromic normocytic anemia
51	18,500	3.5	1.0	Normal	Normal	Pernicious anemia, treated
52	79,500	5.5	0.5	Normal	Normal	Lymphosarcoma
53	39,500	2.5	3.0	Normal	Normal	Bronchiogenic carcinoma, questionable
54	10,250	1.0	0.0	Normal	Normal	Pernicious anemia, treated
57	28,000	5.0	1.0	Normal	Normal	Pernicious anemia, treated
58	17,500	3.0	1.5	Normal	Normal	Metastatic carcinoma, primary unknown
59	37,000	4.0	2.0	Normal	Normal	Carcinoma of the stomach
60	52,000	8.0	7.0	Normal	Normal	Melanoblastoma

Eight cases were classified as showing marked hyperplasia histologically (Table 4). In these the nucleated cell count ranged from 12,500 to 480,000 cells per c.mm., with an average of 185,720 cells per c.mm., and the myeloid-erythroid volume ranged from 2 to 44%, with an average of 17.8%. The volumetric fat content was zero in all cases except 2, in which it was 0.5% and 1% respectively. Histologically fat was either completely absent or markedly decreased in these cases.

Comment. The correlation between the nucleated cell count, the myeloid-erythroid volume and the histologic appearance

hyperplasia, especially in cases of pernicious anemia in relapse. In many cases, either the nucleated cell counts, the myeloid-erythroid volume or both determinations did not correlate with the functional state found on histologic section. Of the 29 cases having a normally active marrow, 3 had nucleated cell counts which were greater than the mean by 40,000 or over and a myeloid-erythroid volume which was more than 4% greater than the mean. Six had counts which were less than the mean by 40,000 or more and 5 of these had a myeloid-erythroid volume which was less than the mean by 4% or more. Seven of the 10 cases classified as being

TABLE 2.—CASES SHOWING HYPOPLASTIC MARROWS HISTOLOGICALLY

Case No.	Volumetric pattern			Histologic pattern		Clinical diagnosis
	Nucleated cell count	Myeloid-erythroid layer	Fat content	Cellularity	Fat content	
1	13,000	1.0	1.5	Hypoplastic	Increased	Aplastic anemia due to tridione
6	38,500	2.0	1.5	Hypoplastic	Normal	Idiopathic thrombocytopenic purpura
10	37,500	3.0	2.5	Hypoplastic	Increased	No diagnosis
21	5,000	0.5	3.0	Hypoplastic	Mark. increased	Aplastic anemia
24	14,000	3.0	1.0	Hypoplastic	Increased	Carcinoma of small intestine with metastasis
28	59,250	5.5	2.0	Hypoplastic	Increased	Pulmonary tuberculosis
32	22,750	2.0	1.0	Hypoplastic	Mark. increased	No diagnosis
33	17,250	2.0	2.0	Hypoplastic	Increased	Questionable brucellosis
34	16,250	1.0	0.0	Hypoplastic	Normal	Miliary tuberculosis
40	22,500	2.0	3.0	Hypoplastic	Increased	Carcinoma of breast with metastases to sternal marrow
44	15,000	1.0	0.0	Hypoplastic	Increased	Lymphosarcoma
47	8,000	2.0	0.0	Aplastic	Decreased	Carcinoma of prostate with metastasis to sternal marrow
49	25,000	2.0	1.0	Hypoplastic	Normal	Possible thyroiditis

TABLE 3.—CASES SHOWING MODERATE HYPERPLASIA HISTOLOGICALLY

Case No.	Volumetric pattern			Histologic pattern		Clinical diagnosis
	Nucleated cell count	Myeloid-erythroid layer	Fat content	Cellularity	Fat content	
18	121,000	5.0	0.0	Mod. hyperplasia	Decreased	Chronic hemolytic anemia
19	125,000	4.0	1.0	Mod. hyperplasia	Normal	Chronic lymphatic leukemia
20	850,000	46.0	4.5	Mod. hyperplasia	Normal	Acute myeloid leukemia
23	51,750	2.0	1.0	Mod. hyperplasia	Normal	Gastro-intestinal malignancy
25	29,250	4.0	0.5	Mod. hyperplasia	Decreased	Pernicious anemia, mild untreated
27	62,000	6.0	0.5	Mod. hyperplasia	Decreased	Micro-erophilic streptococcus infection; possible lupus erythematosus disseminatus
29	42,000	6.0	2.0	Mod. hyperplasia	Normal	Multiple myeloma
36	49,500	5.0	0.25	Mod. hyperplasia	Decreased	Pernicious anemia, mild relapse
45	38,750	3.5	0.5	Mod. hyperplasia	Decreased	Fever of unknown etiology
55	52,500	5.0	0.0	Mod. hyperplasia	Decreased	Hodgkin's disease

TABLE 4.—CASES SHOWING MARKED HYPERPLASIA HISTOLOGICALLY

Case No.	Volumetric pattern			Histologic pattern		Clinical diagnosis
	Nucleated cell count	Myeloid-erythroid layer	Fat content	Cellularity	Fat content	
14	34,750	4.0	0.0	Mark. hyperplasia	Decreased*	Pernicious anemia, severe relapse
15	44,250	4.0	0.0	Mark. hyperplasia	Absent	Pernicious anemia, Case 14, during therapy
16	365,000	28.0	0.0	Mark. hyperplasia	Absent	Chronic myeloid leukemia
17	480,000	40.0	0.0	Mark. hyperplasia	Absent	Chronic myeloid leukemia
43	312,000	44.0	0.0	Mark. hyperplasia	Absent	Polycythemia vera
46	214,000	16.5	0.5	Mark. hyperplasia	Decreased	Idiopathic thrombocytopenic purpura
50	12,500	2.0	0.0	Mark. hyperplasia	Absent	Pernicious anemia, severe relapse
56	23,250	4.0	1.0	Mark. hyperplasia	Decreased	Pernicious anemia, severe relapse

* Markedly.

TABLE 5.—SUMMARY OF DATA

No. cases	Nucleated cell count				Myeloid-erythroid volume				Volumetric fat content	
	Range	Arithmetic mean	σ^1	σm^2	Range	Mean	σ^1	σm^2	Range	Mean
29	6,300-247,000	58,250	50,600	9,390	1.0-17.0	5.0	3.89	0.72	0.25-8.0	1.7
				Normal Marrows						
13	5,000- 59,250	22,615	14,800	4,106	0.5- 5.5	2.1	1.27	0.35	0.0 -3.0	1.4
				Hypoplastic Marrows						
10	29,250-850,000	142,175	250,900	79,300	3.5-46.0	8.65	13.2	4.17	0.0 -4.5	1.0
				Moderately Hyperplastic Marrows						
8	12,500-480,000	185,720	183,100	64,800	2.0-44.0	17.8	17.3	6.13	0.0 -1.0	0.2
				Hyperplastic Marrows						

$$\sigma^1 = \text{Theoretical population variate} = \sqrt{\frac{\sum (\text{Deviation from mean})^2}{(\text{Number of values} - 1)}}$$

$$\sigma m^2 = \text{Standard error of mean} = \frac{\sigma}{\sqrt{\text{Number of values}}}$$

moderately hyperplastic had nucleated cell counts which were less than the mean by 40,000 or more and of these, 5 cases had a myeloid-erythroid volume which was less than the mean by 4% or more. This discrepancy is more apparent than real because the abnormally high values in Case 20 affected the mean unduly in such a small number of cases. In the group of marrows classified as markedly hyperactive, 4 of the 8 cases had nucleated cell counts and myeloid-erythroid volumes which were much lower than the mean. In the hypoplastic marrows, however, no great discrepancies were encountered.

While the mean values for the nucleated cell count and myeloid-erythroid volume were representative of the activity of the marrow, the variations in many individual cases were so great that the functional state of the marrow could not be ascertained with certainty from these examinations alone. Study of histologic sections of the bone marrow is therefore necessary for accurate evaluation of activity.

The manner in which the marrow separates when suction is applied to the aspirating needle probably determines the accuracy with which cell count and volumetric pattern determinations reflect the state of the marrow. If only a few particles separate, or if most of the cells remain in compact or cohesive particles rather than free in the aspirated material, it is obvious that the cell count and myeloid-erythroid content as determined by centrifugation will be erroneously low. The fact that average values for cell count and myeloid-erythroid content compared so well with histologic sections must indicate that in most cases enough cells are free or present in sufficiently small particles that they are included in the cell count and centrifuged specimen. In marrows which for some reason are more cohesive and resist separation into individual cells or small particles, it can be expected that the cell count and volumetric pattern will be erroneously low and will not correlate with the actual

state of the marrow as depicted in tissue sections.

Dilution with peripheral blood, the relative proportion of cells lying free in the sinusoids as opposed to the number fixed in the marrow, as well as the readiness with which cells are detached from the marrow may also affect the nucleated cell count directly and the myeloid-erythroid volume indirectly. In 1 case (Case 11, Table 1), pooling of blood was thought to be a factor in producing abnormally high values inasmuch as the patient was in shock and moribund.

The most striking lack of correlation occurred in patients with pernicious anemia in relapse in whom megaloblastic hyperplasia of the marrow was present (Tables 3 and 4). Study of fixed tissue sections from these cases revealed marked increase in cellularity with a large number of megaloblasts and reduction in the amount of fat as would be expected. Volumetric studies and nucleated cell counts were within normal or less than normal range, however, giving an entirely erroneous picture. Peabody³ has commented on the possibility of megaloblasts being adherent to each other and it seems likely that the marrow in these cases is dense enough to resist withdrawal through the aspirating needle and thus give erroneously low volumetric and cell count values.

The excellent correlation in hypoplastic marrows may be explained by assuming that the inactive marrow yields so few cells that even though factors tending to raise the nucleated cell count operate, the values always remain low.

Correlation between the volumetric fat content and the amount present on histologic section appeared to be completely lacking with the exception of the markedly hyperplastic marrows in which fat was absent volumetrically and histologically. Fat droplets were frequently seen floating free in the aspirated marrow and the amount present probably depended upon the readiness with which it separated from the surrounding tissue.

Summary and Conclusions. The values for the nucleated cell count, myeloid-erythroid volume and fat content obtained from 1 cc. of aspirated sternal bone marrow were compared with the functional state of the marrow as estimated from histologic sections in 60 cases. The correlation between the mean values and the marrow activity was good in the majority of cases, especially in hypoplastic marrows. However, in many cases the nucleated cell count or the myeloid-erythroid volume deviated from the mean by an appreciable amount. This discrepancy was most marked in marrows from patients with pernicious anemia in relapse in whom megaloblastic hyperplasia was present. Although the mean values for

the nucleated cell count and myeloid-erythroid volume are representative of the activity of the bone marrow in a group of cases, the individual values may vary so greatly that the functional state of the marrow cannot be assayed with certainty from these findings in any one case. Study of histologic sections is therefore necessary for accurate evaluation of the bone marrow activity in individual cases. There appeared to be no correlation between the volumetric fat content and the amount of fat present in the histologic sections of the marrow with the exception of the hyperplastic marrows, in which fat was markedly reduced or absent. Some of the factors which may have accounted for the lack of correlation were discussed.

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THE BLOOD LACTATE-PYRUVATE RELATIONSHIP IN VARIOUS
PHYSIOLOGIC AND PATHOLOGIC STATES*

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RECENT investigations have shown that pyruvic acid and lactic acid accumulate in the blood and tissues when carbohydrate is being metabolized at an increased rate, in anoxia and following exercise.⁴⁻⁹ Lactic acid, an intermediate product in the metabolism of carbohydrate, is produced in large amounts under anaerobic conditions. Further breakdown leads to the formation of pyruvic acid, which requires diphosphothiamine and oxygen for utilization. In thiamine deficiency, pyruvic acid accumulates in the blood and tissues and there is a change in the quantitative relationship of lactic to pyruvic acid. Stotz and Bessey⁹ found that the blood lactate-pyruvate ratio was relatively constant in normal animals but was reduced in experimental thiamine deficiency. Keys and co-workers⁸ reported a change in the relationship of lactic to pyruvic acid in the blood in men on a restricted intake of the B vitamins. Friedemann⁴ suggested that the blood lactate-pyruvate relationship may reflect the relative oxidative conditions of the body. Horwitt *et al.*⁷ have pointed out the influence of environmental and other factors on the levels of lactic and pyruvic acids in the blood.

This investigation was undertaken to study further the effect of certain physiologic changes on the concentrations and relationship of lactic and pyruvic acids in the blood in normal persons and in patients with various pathologic states and to ascertain whether determination of the

lactate-pyruvate ratio might assist in the detection of human thiamine deficiency.

Methods. The subjects of this study were 29 presumably normal persons (physicians, technicians and medical students) and 41 patients who were being treated for various diseases in the medical clinics of Tulane University or in the medical wards of Charity Hospital in New Orleans. Lactic and pyruvic acids in the blood were determined during fasting, after meals, after the administration of glucose, during rest, following light and strenuous exercise and, in a few instances, following electric shock therapy. Glucose was given orally (100 gm.) or intravenously (50 gm.), following which blood was collected at intervals for 2 to 3 hours. Light exercise consisted in carrying on routine work in the laboratory or hospital, strenuous exercise in running down and up 3 flights of stairs as rapidly as possible. Blood was collected within 5 to 15 minutes after strenuous exercise or electric shock therapy.

Pyruvic acid was determined by the method of Bueding and Wortis.² While keto-acids other than pyruvic contribute to the findings with this procedure, the designation "pyruvic acid" will be used throughout this paper. The method of Barker and Summerson¹ was used in determining lactic acid.

Approximately 6 cc. of blood was collected from an arm vein with a syringe, care being used to avoid stasis. Three cc. was immediately placed in each of 2 bottles, 1 containing potassium oxalate, the other potassium oxalate and sodium iodoacetate. From each bottle 2 cc. was transferred with a pipette to a flask containing 10% trichlor-

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acetic acid. These manipulations were carried out at the side of the patient and only a few minutes were required for precipitation of the blood. All equipment was kept in a refrigerator prior to use. Sodium iodoacetate was added to the anticoagulant in the determination of pyruvic acid, since it retards the breakdown on this substance, but was omitted from the determination of lactic acid due to interference in this procedure.

FINDINGS IN NORMAL PERSONS. The levels of pyruvic and lactic acids in the blood and the lactate-pyruvate ratios which were found in normal persons under conditions of rest, exercise and alimentation are given in Table 1. In the basal

engaged and the time which had elapsed since breakfast. The concentrations of lactic and pyruvic acids may not return to the fasting level for 3 or more hours after a meal.

Following the administration of glucose there was an increase in both pyruvic and lactic acids in 9 of 10 subjects. The maximum rise was observed after an interval of 30 to 60 minutes in 6 instances and after 90 to 120 minutes in 3. The concentrations of these metabolites returned to the level observed during fasting at the end of 2 to 3 hours. The lactate-pyruvate ratio was essentially the same as that found in the basal state.

Following a brief period of strenuous

TABLE 1.—BLOOD PYRUVIC AND LACTIC ACIDS AND THE LACTATE-PYRUVATE RATIO IN NORMAL SUBJECTS

Test conditions	No. subjects	Pyruvic acid (mg. per 100 cc.) (mean)	Lactic acid (mg. per 100 cc.) (mean)	Lactate-pyruvate ratio	
				Mean	σ
Fasting, resting	21	1 00	9 3	9 3	± 1.7
Fasting, light exercise	8	1 09	10 1	9 3	± 2.3
After breakfast, light exercise . .	24	1 06	10 5	10 0	± 3.4
After glucose ($\frac{1}{2}$ to 1 hr.)	11	1 40	13 0	9 3	± 2.1
After glucose ($1\frac{1}{2}$ to 2 hrs.) . . .	9	1 32	12 2	9 3	± 1.5
After strenuous exercise	29	1 96	35 0	18 3	± 3.5
After electric shock	9	2 96	49 6	18 0	± 5.8

state the mean findings in 21 persons were pyruvic acid 1 mg. per 100 cc., lactic acid 9.3 mg. per 100 cc., and a lactate-pyruvate ratio of 9.3, with a standard deviation of ± 1.7 . In 1 person the level of pyruvic acid was 1.3 mg. which is considered to be the upper limit of normal and the lactate-pyruvate ratio was found to be 5.1. In all other persons examined, ratios of more than 7.3 were obtained.

After light exercise in the fasting state, the findings were similar to those obtained at rest, although the mean concentration of lactic acid was slightly increased. After light exercise taken 2 or 3 hours after breakfast there was again an increase in blood lactic acid while pyruvic acid was unchanged. There was consequently a slight rise in the lactate-pyruvate ratio. The increase in the variability of findings and the slightly elevated ratio were probably due to 2 factors: the amount of physical activity in which the subject had

exercise there was a moderate increase in pyruvic acid and a marked increase in lactic acid in all instances. The greatest increase in lactic and pyruvic acids and in the lactate-pyruvate ratio occurred 5 to 15 minutes after exercise. Following this there was a gradual decline, but values were still high at the end of 30 minutes.

After electric shock therapy in which convulsive seizures were produced lactic and pyruvic acids in the blood increased to an extent greater than that observed after strenuous exercise but the mean lactate-pyruvate ratio was essentially the same. Two factors appear to be responsible for the rise in lactic and pyruvic acids under these circumstances: anoxia and muscular activity. In a few patients electric shock failed to induce a convulsive seizure. In these instances there was rise in both lactic and pyruvic acids, but the increase was less marked than when muscular contractions occurred.

The above findings are similar to those reported by other investigators. Bueding, Wortis and Stern³ found an average concentration of pyruvic acid of 0.98 mg. per 100 cc. in 60 adults examined under basal conditions. Friedemann⁴ tested subjects at rest 3 to 5 hours after a meal and reported a mean concentration of pyruvic acid of 0.77 mg., of lactic acid 8.5 mg. and a lactate-pyruvate ratio of 11.3. Pyruvic acid was determined without the use of iodoacetate, which may account for the lower values obtained for this metabolite.

The increase in concentration of both pyruvic acid and lactic acid after the administration of glucose, following strenuous exercise and subsequent to electric shock therapy, are corroborative of the findings of Friedemann *et al.*⁴ who concluded that food, exercise and anoxia were the most important factors influencing the concentration of lactic and pyruvic acids in the blood in normal persons.

In view of the marked effect of exercise on lactic acid values, test conditions should be rigidly standardized if the lactate-pyruvate ratio is to be used in studying fundamental oxidative changes in the body. Findings similar to the basal state may be obtained 3 or more hours following a meal and after a rest period of 30 minutes or more, the time depending on the severity of the previous exercise.

In experiments on rats, pigeons and man, Stotz and Bessey⁹ concluded that the lactate-pyruvate ratio is relatively constant in normal animals and can be expressed graphically or by formula. Friedemann⁴ questioned the constancy of this relationship. The lactate-pyruvate ratios which we obtained in normal persons under various physiologic conditions are illustrated in Figure 1. A relatively constant relationship is observed in the basal state and there is little change after mild exertion, a meal, or the administration of glucose. Strenuous exercise and electric shock therapy produce a shift in the ratio and wider variation in values but the points still fall essentially along

a straight line. These observations confirm in principle the observations of Stotz and Bessey, although the mathematical relationships are somewhat different.

Stotz and Bessey⁹ suggested expressing the lactate-pyruvate relationship in terms of pyruvic acid values so that a single figure might indicate the degree of disturbance of pyruvate metabolism. Formulae for calculating the expected level of pyruvic acid, from the value of lactic acid found by analysis, are included in Figure 1. For example, in the basal state, pyruvic acid (calculated) = $\frac{\text{Lactic acid} - 1.08}{8.17}$.

Pyruvate excess is determined by subtracting the pyruvic acid calculated from the pyruvic acid found by chemical analysis. In normal pigeons Stotz and Bessey⁹ found that values for pyruvic acid (PA) excess varied from -0.27 to $+0.29$ mg. per 100 cc. On a thiamine-free diet a large increase in PA excess values was observed. Determination of PA excess was useful in detecting mild degrees of chronic thiamine deficiency.

Values for PA excess for the normal persons in this study ranged from -0.53 to $+0.59$ mg. per 100 cc. in the basal state. In only 1 instance, however, was an excess of more than 0.3 mg. observed. Following either light or strenuous exercise approximately one-fourth of the subjects were found to have values for PA excess which were greater than 0.3 mg. Such values may indicate a disturbance of metabolism due to thiamine deficiency or may merely reflect variation in the normal response to exercise dependent on training and physical fitness. Friedemann⁴ found a greater rise in pyruvic acid after stair climbing in women whose diets were low in thiamine than in persons whose diets were adequate. Keys⁸ observed a similar increase in pyruvic acid following exercise in men on diets low in the B group of vitamins. An exercise test may be useful in detecting mild degrees of thiamine deficiency, but further investigation is needed, using a standardized

procedure, before a definite conclusion can be reached.

FINDINGS IN PATIENTS WITH VARIOUS DISEASES. Lactic and pyruvic acids were measured in the blood of 41 patients with various diseases. Table 2 gives the findings obtained under basal conditions and includes those of normal subjects for comparison. In patients with a deficiency of thiamine, or of riboflavin or niacin, mean pyruvic acid was elevated above the normal and there was a decrease in the mean lactate-pyruvate ratio. In patients with heart disease mean pyruvic

acid was slightly increased and mean lactic acid decreased with resultant lowering of the ratio of these metabolites.

In 19 patients with various afebrile conditions the mean lactate-pyruvate ratio was essentially normal. Of this group of patients there were 3 in whom pyruvic acid was greater than 1.3 mg. per 100 cc. In 2 of these, however, the lactate-pyruvate ratio was normal. In the third the ratio was low (less than 7) and pyruvate excess was greater than 0.3 mg. In this patient, who had a contact dermatitis, the diet had apparently been adequate

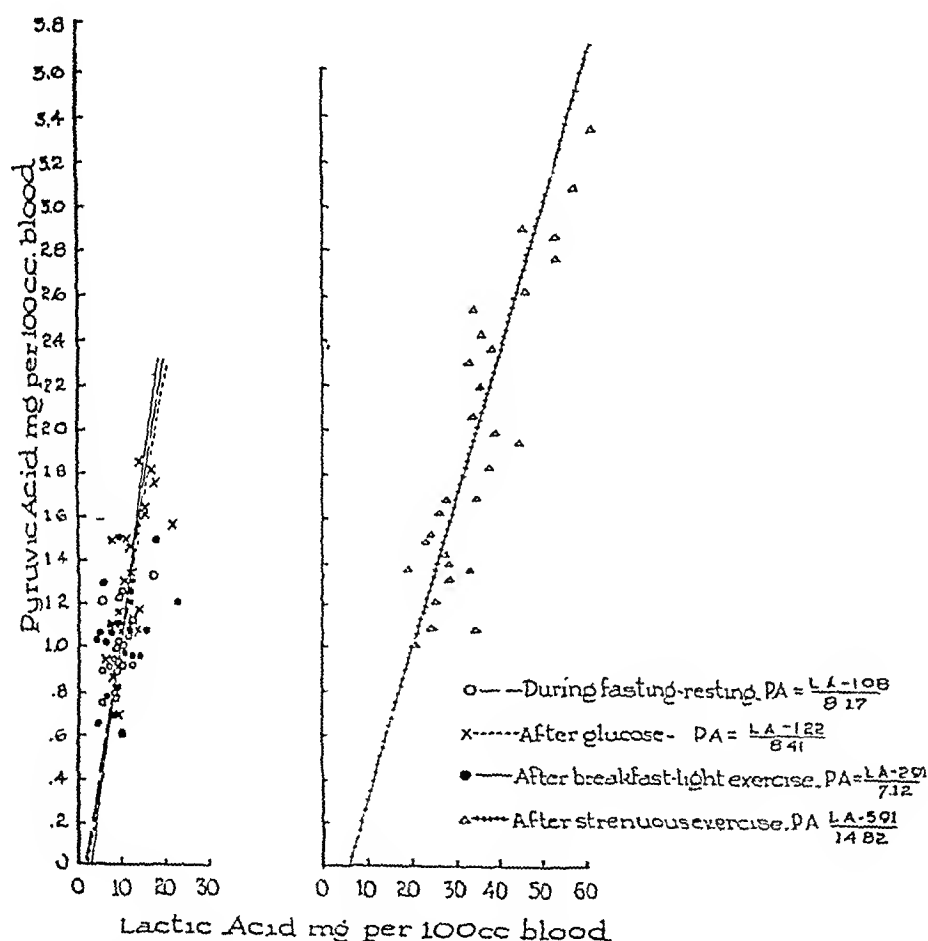


FIG. 1. The lactate-pyruvate relationship in normal persons—at rest, after eating and after exercise.

TABLE 2.—THE RELATIONSHIP OF PYRUVIC AND LACTIC ACIDS IN THE BLOOD IN THE BASAL STATE IN NORMAL SUBJECTS AND IN PATIENTS WITH VARIOUS DISEASES

Diagnosis	No. subjects	Pyruvic acid (mg. per 100 cc.)	Lactic acid (mg. per 100 cc.)	Lactate-pyruvate ratio
Normal	21	1.00	9.3	9.3
Thiamine deficiency	6	1.34	9.2	6.9
Riboflavin and niacin deficiency	7	1.26	10.0	7.9
Heart disease	9	1.16	8.6	7.8
Miscellaneous diseases	19	1.06	10.0	9.7

and there was no clinical evidence of deficiency disease. One patient in whom the diagnosis of peptic ulcer was made, had a normal lactate-pyruvate ratio during fasting and a low ratio after the administration of glucose. The diet of this patient had been somewhat low in vitamins of the B complex.

Individual findings in the 6 patients who had clinical evidence of thiamine deficiency are shown in Table 3. Three patients had an increase in pyruvic acid above 1.3 mg. In all patients the lactate-pyruvate ratio was somewhat low and in 3 instances it was less than 7. Pyruvate excess was greater than 0.3 mg. in 4 patients. Glucose was administered to 3 patients (Cases 1 to 3) and in each instance the lactate-pyruvate ratio and pyruvate excess was similar to that of the basal state. The diet of each of the 7 patients with thiamine deficiency had been low in all of the B vitamins, although in 1 instance (Case 2) there had been recent improvement in the food intake. This may account for the relatively normal

biochemical findings although peripheral neuritis was still present.

One patient (Case 1) was especially interesting in that 5½ weeks prior to examination she had delivered a child who was diagnosed as having congenital beriberi.¹⁰ Her diet during the last 3 months of pregnancy had been limited to fruit, bread and 1 cup of milk daily. She resumed her normal diet for 3 weeks following delivery and then returned to the deficient diet. Signs of mild thiamine deficiency were still present at the time of biochemical testing but were less severe than at the termination of pregnancy.

This patient (Case 1) and another (Case 5) were retested after thiamine had been administered for 14 and 7 days respectively. Clinical improvement had occurred and there was a marked change in biochemical findings in both patients (Table 4).

In the 7 patients with niacin and/or riboflavin deficiency (Table 5) pyruvic acid was elevated in 3, the lactate-pyruvate ratio was below 7 in 2, and pyruvate

TABLE 3.—THE RELATIONSHIP OF LACTIC ACID AND PYRUVIC ACID IN THE BLOOD IN PATIENTS WITH THIAMINE DEFICIENCY

Case No.	Clinical findings	Pyruvic acid (mg. per 100 cc.)	Lactic acid (mg. per 100 cc.)	Lactate-pyruvate ratio	Pyruvate excess (mg. per 100 cc.)
1	Neuritis-edema-dyspnea	1.16	8.0	6.9	+0.32
2	Neuritis-cirrhosis of liver	0.90	6.9	7.7	+0.18
3	Mild neuritis	1.21	7.1	5.9	+0.47
4	Mild neuritis	1.81	11.2	6.2	+0.57
5	Neuritis-hepatitis, cerebral symptoms	2.15	16.0	7.4	+0.39
6	Mild neuritis	0.81	6.2	7.6	+0.19
Mean		1.34	9.2	6.9	+0.35

TABLE 4.—EFFECT OF THIAMINE ADMINISTRATION ON BLOOD PYRUVIC AND LACTIC ACIDS AND ON THE LACTATE-PYRUVATE RATIO

Diagnosis	Time (days)	Amt. B ₁ daily (mg.)	Pyruvic acid (mg. per 100 cc.)	Lactic acid (mg. per 100 cc.)	Lactate-pyruvate ratio	Pyruvate excess (mg. per 100 cc.)
Thiamine deficiency	0	0	1.16	8.0	6.9	+0.32
	14	60	0.52	5.2	10.1	+0.01
Thiamine deficiency	0	0	2.15	16.0	7.4	+0.39
	7	30	1.08	7.8	7.3	+0.25
Hyperthyroidism, niacin and riboflavin deficiency	0	0	1.45	9.0	6.2	+0.48
	1	50	1.96	14.2	7.2	+0.42
	2	50	1.03	8.8	8.6	+0.08
Heart disease	0	0	1.08	7.4	6.8	+0.31
	14	30	1.03	9.1	8.8	+0.05
Heart disease	0	0	1.35	10.1	7.4	+0.25
	14	30	1.06	12.2	11.5	-0.23

excess measured 0.3 mg. or more in 3 instances. This is not an unexpected finding, since deficiency of any one of the B vitamins is usually associated with a deficiency of other members of the group. The diet of each of these subjects had been somewhat low in thiamine as well as in riboflavin and niacin. One patient, Case 2, had hyperthyroidism as an additional etiologic factor in the production of a deficiency state. She was treated with a large amount of thiamine as shown in Table 4 (Case 3) and within 2 days pyruvic acid and the lactate-pyruvate ratio had returned to normal.

in whom thiamine excretion was low, there was an excess of pyruvate in the blood.

The relationship of pyruvic and lactic acids in the blood in 9 patients with heart disease is shown in Table 6. Pyruvic acid was elevated in 3 subjects, while the lactate-pyruvate ratio was below 7 and pyruvate excess was greater than 0.3 mg. in 4. Glucose was given to 4 patients and corroborated the findings obtained during fasting. The abnormalities of pyruvate metabolism did not appear to be related to the presence of heart failure or to its severity. These findings differ from those

TABLE 5.—THE RELATIONSHIP OF LACTIC ACID AND PYRUVIC ACID IN THE BLOOD IN PATIENTS WITH RIBOFLAVIN AND NIACIN DEFICIENCY

Case No.	Clinical findings	Pyruvic acid (mg. per 100 cc.)	Lactic acid (mg. per 100 cc.)	Lactate-pyruvate ratio	Pyruvate excess (mg. per 100 cc.)
1	Glossitis-cheilosis	1.03	3.8	3.7	+0.70
2	Glossitis-cheilosis	1.45	9.0	6.2	+0.48
3	Glossitis	1.43	11.1	7.9	+0.23
4	Glossitis-cheilosis	1.26	12.4	9.8	-0.13
5	Mild glossitis	1.09	12.7	11.6	-0.28
6	Cheilosis	1.38	12.4	9.0	+0.05
7	Glossitis	1.16	8.5	7.3	+0.30
	Mean	1.26	10.0	7.9	+0.19

TABLE 6.—THE RELATIONSHIP OF PYRUVIC ACID AND LACTIC ACID IN THE BLOOD IN PATIENTS WITH HEART DISEASE

Subject No.	Heart failure	Pyruvic acid (mg. per 100 cc.)	Lactic acid (mg. per 100 cc.)	Lactate-pyruvate ratio	Pyruvic acid excess (mg. per 100 cc.)
1	+	1.72	4.6	2.7	+1.29
2	+	1.35	10.0	7.4	+0.25
3	-	1.08	7.4	6.8	+0.31
4	+	1.10	6.8	6.2	+0.39
5	-	0.73	7.3	10.0	-0.03
6	+	1.08	10.7	9.9	-0.05
7	-	0.94	11.8	12.5	-0.37
8	-	1.36	9.2	6.8	+0.37
9	+	1.12	9.1	8.1	+0.14
	Mean	1.16	8.6	7.8	+0.26

The urinary excretion of thiamine was determined in 9 of the 13 patients with evidence of deficiency of one or more of the B vitamins. In the patients with signs of thiamine deficiency, a low excretion was found in 3 (Cases 1, 5 and 6), a normal output in 1 (Case 4). In 5 patients with niacin and riboflavin deficiency the excretion of thiamine was low in 2 instances (Cases 2 and 5), normal in 3 (Cases 3, 6 and 7). In 4 of the 5 patients

of Yanof,¹¹ who reported a rise above normal of pyruvic acid in the blood of patients with heart failure, the elevation approximating the degree of failure. Lactic acid was not determined in his study.

Two patients with heart disease (Cases 1 and 3) had signs of a mild peripheral neuritis suggestive of thiamine deficiency. The diet had been poor in both subjects but particularly so in Subject 1. In 3 other patients (Cases 7, 8 and 9) the

dietary history indicated an inadequate intake of foods containing vitamins of the B complex. In the remaining patients the diets could be classified as fair. In our experience, heart disease with failure is one of the commonest precipitating causes of deficiency disease. Anorexia and poor absorption and utilization of nutrients are probably responsible for this.

Two patients with heart disease, in whom the lactate-pyruvate ratio was low, were treated with thiamine and retested after 2 weeks (Table 4). A definite increase in the ratio and a decrease in pyruvate excess followed therapy. Two other patients were tested for the first time after thiamine had been prescribed for several days. The ratios were found to be 8.6 (normal) and 14.7 (slightly elevated).

These data suggest that the low lactate-pyruvate ratio found in 4 of 9 patients with heart disease was due to a deficiency of thiamine. This deficiency may have been primarily of dietary origin or may have been a relative deficiency resulting from metabolic changes of anoxia associated with heart disease. In anoxia, lactic acid is usually increased to a greater extent than is pyruvic acid. However, a dephosphorylation of cocarboxylase and a decrease in other enzyme systems have been shown to occur in anoxic states.⁶ Govern, Greer and Greig^{5,6} have found that the administration of thiamine leads to a reduction of pyruvic acid in experimental shock and anoxia. Whether these findings are of importance in the production of thiamine deficiency in heart disease, or in the lactate-pyruvate ratio which was observed in this condition, is unknown.

In this study a dietary deficiency of

thiamine appears to be a reasonable explanation of the findings. If this conclusion can be substantiated in a larger group of patients, determination of the lactate-pyruvate ratio should be a useful procedure in the diagnosis of beriberi heart disease or of thiamine deficiency in association with heart disease of varied etiology.

Summary. The relationship of lactic acid to pyruvic acid in the blood was studied in 29 normal persons and in 41 patients with various diseases. In normal persons the lactate-pyruvate relationship can be expressed graphically or by formula for a given physiologic state. Under basal conditions a mean ratio of 9.3 was obtained. This ratio was essentially unchanged following the administration of glucose. Exercise produced an increase in the ratio the extent being dependent upon the degree of physical activity.

In patients with clinical evidence of deficiency of thiamine the lactate-pyruvate ratio was decreased. A low ratio was also observed in approximately half of the patients with riboflavin and niacin deficiency and of the patients with heart disease. Following the administration of thiamine the ratio returned to normal. In a group of miscellaneous afebrile conditions the lactate-pyruvate ratio was essentially normal. Thiamine deficiency is suggested by a lactate-pyruvate ratio of less than 7, or by an excess of blood pyruvate of more than 0.3 mg. per 100 cc. above the value calculated from the normal ratio at the lactic acid level found.

Determination of the relationship of lactic and pyruvic acids in the blood may be of assistance in evaluating thiamine nutrition in complicated pathologic states.

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THE RELATIONSHIPS OF PERIPHERAL VENOUS PRESSURES TO PULMONARY TUBERCULOSIS

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INVESTIGATION of the peripheral venous pressures in patients with pulmonary tuberculosis was begun at this hospital without any attempt to select cases. Gradually, however, a precise field of clinical usefulness for the test became evident. In the course of this work, determinations on several patients under unusual conditions yielded results of special significance, and these will be reported below.

Deviations of venous pressure from the normal as a result of collapse therapy have been observed by numerous investigators. One would anticipate such deviations from the fact that intrathoracic pressure influences the filling of the right auricle and hence affects the peripheral venous pressure.⁹ That this cannot be the only mechanism operative in these cases has been shown by investigators who have made bilateral venous pressure determinations and observed abnormal readings on 1 side only.^{10,12} In practice, the changes are by no means constantly present, but the anatomic and physiologic mechanisms involved are of interest.

VENOUS PRESSURES IN CASES OF THORACOPLASTY. Overholt and Pilcher¹² found a correlation between unilateral elevation of venous pressure following thoracoplasty and poor toleration of the collapse procedure, as manifested by dyspnea, cyanosis, rapid pulse, and in some cases paradoxical movements of the chest wall. They attached prognostic significance to such elevations and waited until the venous pressure fell to normal before proceeding with the operation. Coryllos and

Stanford² found a postoperative rise on the side of the operation in about two-thirds of 34 patients, which they attributed to dropping of the axillary vein with local obstruction (of no prognostic significance). Hurst and Brand¹⁰ arrived at similar conclusions. Feinsilver³ found no significant difference between the preoperative and postoperative levels of venous pressure in 14 cases of thoracoplasty. He believed the postoperative rise observed by Overholt and Pilcher to be a temporary phenomenon which disappears by the 3rd month. In any case, Overholt and Pilcher concluded that an elevated venous pressure indicated excessive degree of collapse and that there is little likelihood of disturbing a normal preoperative venous pressure if no more than 3 or 4 ribs are removed in the first stage. Since these limits are rarely exceeded in modern surgical practice, the postoperative unilateral rise in venous pressure is probably largely of historical interest.

VENOUS PRESSURES IN CASES OF INTRA-PLEURAL PNEUMOTHORAX. In artificial intrapleural pneumothorax, changes in venous pressure are likewise not constantly present. Grellety-Bosviel,⁵ in a large series of cases with unilateral pneumothorax, found the venous pressure unchanged in 85%. In the remaining 15%, there was a temporary rise in the venous pressure, which he attributed to a diminution of lung substance and compression of the pulmonary vessels with stasis in the right chambers of the heart. Hurst and Brand¹⁰ reported 21 cases of pneumothorax fol-

lowed, either before and after the induction of collapse, or during the course of collapse, and of these, 11 showed changes in venous pressure. The changes fell into the following general patterns: Atelectatic retracted lungs with high venous pressure on the homolateral side may show, after pneumothorax, a reduction in venous pressure by the release in pull on the venous return in the subclavian or innominate veins; high tension pneumothorax may cause a rise in venous pressure on that side, and effusions may act in a similar fashion, by causing a rise in intrapleural pressure. Feinsilver,³ on the basis of observations in 15 cases of pneumothorax, concluded that "although a rise in venous pressure is not the rule in pneumothorax, it does occur frequently, at least as a temporary phenomenon." Heise and Steidl⁷ came to the conclusion that fluid, pneumothorax, and thoracoplasty give rise to rare elevations of venous pressure, and usually such elevations are unilateral.

VENOUS PRESSURE IN CASES OF EXTRAPLEURAL PNEUMOTHORAX. The literature on venous pressure in extrapleural pneumothorax is very meager. One might anticipate deviations from the normal to follow the same pattern as for intrapleural pneumothorax. Feinsilver³ reported venous pressures in 3 extrapleurals, 2 to 3 months before surgery and 2 to 4 months after surgery. One (bilateral) case showed no change. One case showed a bilateral reduction in venous pressure of significant degree and 1 (bilateral) case showed a bilateral elevation of questionable significance.

Method. The method for obtaining venous pressures used in our series was that of Taylor, Thomas and Schleiter¹⁵ as modified by Hitzig.⁸

The patient rests in the supine position with the relaxed arm supported in slight abduction on a pillow, so that the antecubital surface is 5 cm. below the anterior chest wall at the insertion of the fourth rib. This is assumed to be the level of the caval openings into the right auricle. A tourniquet or blood pressure cuff is applied, a

large vein is selected and venipuncture performed with an 18-gauge needle attached to a 2-cc. syringe. When the bevel of the needle rests freely in the vein, the syringe is detached, and an L-shaped tube calibrated in half-centimeters, the inside of which has been moistened with sterile 5% sodium citrate solution, is attached and the level at which the blood column stops mounting is noted. Tiny respiratory oscillations are usually apparent and are evidence of a freely patent system.

A few of our more recent determinations were done with the method used by Overholt and Pilcher.¹² In this technique, a 3-way stopcock is interposed between the needle and the syringe, and a spinal manometer tube is attached to the stopcock. Citrate solution from the syringe is injected into the tube and by turning the stopcock to communicate the tube with the vein, the citrate solution is allowed to run into the vein (or blood into the tube) until equilibrium is established. The 2 methods, L-tube and 3-way stopcock with manometer tube, have been shown to give virtually identical results, but the latter has some advantages in permitting easy determination of circulation times *via* the same needle and repeated determinations of venous pressure without clotting. Both methods suffer seriously from the need for using a large gauge needle. All too frequently it is difficult or impossible to find a vein capable of receiving such a needle. An ingenious new apparatus for obtaining venous pressure has been devised by Winsor and Burch.¹⁷ When commercially available, this "phlebomanometer" should greatly extend the usefulness of venous pressure determinations, since it makes possible precision determinations with the finest gauge needles.

As the upper limit of normal we took 10 cm. and no distinction was made between male and female patients. This value for normal is based on Hitzig's findings in 624 normal subjects (in whom normality was confirmed by arm-to-tongue and arm-to-lung circulation times). Of these subjects, 93.2% had venous pressures in the range of 4 to 8 cm. The remainder fell within the low range of 2 to 4 cm. (4.3%) or the high range of 8 to 10 cm. (2.5%).

Results and Discussion. With regard to the general relationship of peripheral

venous pressure to pulmonary tuberculosis and collapse therapy, suffice it to say that observations in 55 patients lead us to conclusions quite similar to those of previous investigators. Deviations from the normal are the exception rather than the rule, are observed most often unilaterally and usually on the side of more disease or collapse, and may be transient.

VENOUS PRESSURES IN CASES OF EXTRAPLEURAL PNEUMOTHORAX. Table 1 shows data obtained in 4 cases of extrapleural pneumothorax. For purposes of study, the extrapleural pneumothorax is of unique advantage in that intrathoracic pressures can be raised to levels seldom reached in present-day intrapleural pneumothorax.

The only comparable study in the literature offers interesting contrasts in method and theoretical interpretation, yet with considerable similarity in results. Holt⁹ was concerned primarily with determining whether peripheral venous pressure is a function of right auricular pressure in man. He had his (normal) subjects breathe through a mouthpiece from a breathing chamber in which the pressure could be varied from 20 cm. of water above to 20 cm. below atmospheric pressure, while peripheral venous pressures were simultaneously recorded.

If our venous pressure data in Case 3 (Table 1) be plotted (Fig. 1) on coördinates of same scale as used by Holt, a

TABLE 1.—VENOUS PRESSURES (V.P.'s) IN CASES WITH EXTRAPLEURAL PNEUMOTHORAX

Case	Extrapleural pressure*	V.P. collapsed side	V.P. uncollapsed side
1. C. P.†	+44, +48	7	4
2. C. G.	-5, -2	6½	8½
	After injection of 300 cc. of air: +18, +20	11½	6½
3. S. K.	-13, -1	5	
	After injection of 200 cc. of air: -2, +2	5	
	After injection of 400 cc. of air: +10, +12	9	
	After withdrawal of 400 cc. of air: -2, +1	5	
	After injection of 300 cc. of air: +6, +10	7½	
	After injection of 400 cc. of air: +16, +20	11	
	After removal of 400 cc. of air: -2, 0	5	
4. L. W.	-5, -2	13½	6½
	After injection of 300 cc. of air: +18, +20	16½	6½

* Measured in centimeters of water relative to atmospheric pressure.

† Case C. P. is not comparable to the others, in that venous pressures and extrapleural pressure determinations were not made simultaneously, hence the actual relationship between the 2 is not known.

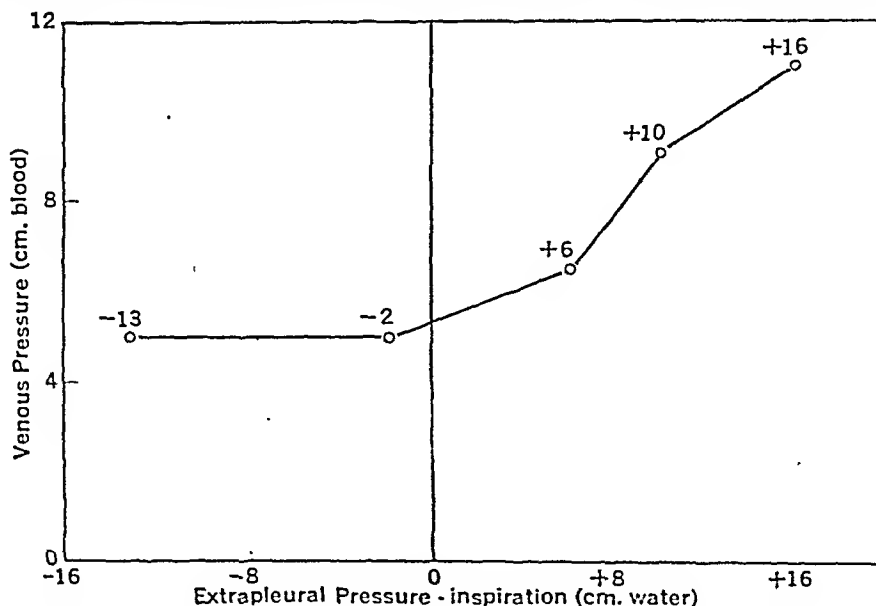


Fig. 1.—Graph correlating venous pressure and extrapleural pressure.

linear relationship of very similar slope to that which he found becomes evident. The unchanged venous pressure in the face of varied sub-atmospheric intrathoracic pressures is to be attributed, we believe, to the partial collapse of the peripheral veins when intrathoracic pressures become markedly negative. Such a phenomena is described by Holt and may well explain the occurrence of normal venous pressures with high negative intrapleural pressures observed by all workers in this field. On the other hand, the magnitude of positive intrathoracic pressure changes necessary to produce rather small changes in venous pressure explains, we believe, why elevations of venous pressure are only occasionally observed in the course of collapse therapy.

VENOUS PRESSURES IN CASES WITH DYPNEA. Table 2 summarizes our findings in 30 patients, all of whom showed more or less dyspnea at rest. All had a considerable amount of intrapulmonary disease but in most instances the usual clinical and Roentgen ray signs of right heart failure were absent or only equivocal. The generally bad prognostic import of a persistently elevated venous pressure and positive Pasteur-Rondot phenomenon in spite of therapy is apparent. Only exceptionally could surgery be contemplated in such a patient.

It is in this group of patients with dyspnea that venous pressure determinations offer invaluable information as to presence or absence of early heart failure as a component in the clinical picture, and this information is not readily available in any other way. The "dynamic" methods of demonstrating impaired cardiac reserve, involving as they do rapid infusions or exercise, are not without hazard. Circulation time determinations might help, but the interpretation of results would be complicated in some cases by the fact, demonstrated by Feinsilver,³ that arm-to-lung time is significantly reduced by any type of collapse therapy. On the other hand, the factor of presence of collapse therapy does *not* interfere with interpre-

tation of venous pressures for 2 reasons: (1) Variations in venous pressure due to collapse procedures are almost invariably unilateral. (2) Use is made of the "hepato-jugular reflux" of Pasteur and Rondot,^{13,14} as recently applied to venous pressure determinations by Hitzig.⁸ This phenomenon, which is never observed with venous pressure alterations due simply to collapse procedures, is pathognomonic of right heart insufficiency, even when the initial venous pressure is within normal limits.

Briefly, the test consists of sustained and gradually increasing manual compression of the right upper quadrant while the patient is instructed to breathe normally with the mouth open. With the manometer attached, the venous pressure is recorded at the end of 1 minute of sustained pressure. In the presence of a normally functioning right ventricle, the pressure remains unchanged or falls slightly. A rise in pressure is a sensitive indicator of right ventricular weakness. For an explanation of these phenomena the reader is referred to Hitzig's paper.⁸

The need for a means of differentiating cardiac from pulmonary insufficiency, or at least of recognizing a cardiac component in a given case, is very real. Griggs, Coggin and Evans⁶ found that of 1470 cases of tuberculosis coming to autopsy, 3.7% showed right ventricular hypertrophy, and 1.8% showed definite congestive failure. Due to the high incidence of tuberculosis, right ventricular hypertrophy was seen more frequently (18,000 consecutive autopsies) in patients with tuberculosis than with any other pulmonary disease.

Chronic pulmonary tuberculosis may result in pulmonary circulatory changes either by its destructive action, by parenchymal fibrosis, by the effects of associated emphysema, or secondary to collapse measures.^{1,11} All these may produce venous pressure changes directly, as discussed above, or the venous pressure may rise secondarily when the strain on the right heart results in cardiac insufficiency. Weiss and Blumgart,¹⁶ and Fishberg⁴ found

TABLE 2.—VENOUS PRESSURES* IN PATIENTS WITH DYSPNEA

Case	Date	Right arm		Left arm		Remarks
		Initial V.P.	Pasteur-Rondot	Initial V.P.	Pasteur-Rondot	
1. G. B.	4/17/47	5	7	5	8	Normal V.P.'s with positive P-R phenomenon; cardiac insufficiency is anticipated
2. M. B.	8/15/46	5	5	7	7	Normal V.P.'s; severe dyspnea due to asthma and pulmonary emphysema
3. T. B.	9/18/46	11	12½	9	13	V.P.'s upper limit of normal with positive P-R phenomenon; other evidence of cardiac insufficiency soon appeared; died
4. M. C.	2/ 7/46	5	4½	5	4½	Normal V.P.'s; in spite of severe dyspnea, the result of extensive destruction, maintains status quo as a "good chronic"
5. N. E.	5/13/46	10	10½	13	15	Elevated V.P.'s and positive P-R phenomenon; circulation times on same date normal; subsequent course points toward anticipated cardiac failure
6. D. F.	6/ 6/47	8½	8½	Normal V.P.; dyspnea due to disseminated pulmonary disease
7. A. G.	11/ 5/45 1/ 4/46 12/31/46	7 17 30†	9 24	5	7½	First V.P.'s normal but P-R phenomenon positive; cardiac insufficiency thus anticipated and actually ensued; responded temporarily to treatment but died in failure 4/7/47
8. B. H.	1/22/47 5/27/47	15 10	17 10	15 8½	17 8½	V.P.'s normal; dyspnea due to "frozen" right lung and disseminated disease
9. B. H.	4/ 8/46	15	17	7	9½	Elevated V.P. on right (thoracoplasty) side; P-R phenomenon positive bilaterally; has subsequently survived 2 more surgical stages, but clinical course has been exceedingly precarious
10. M. H.	1/ 6/45 4/ 1/46 11/ 2/46	10½ 12 15	9½ 18 16	10 13½	9½ 14	Progressive elevation of V.P.'s and appearance of positive P-R phenomenon; definite clinical evidence of right heart failure did not appear until 1/2/47, 10 days before death
11. J. H.	6/19/46	14½	18	Elevated V.P. and positive P-R phenomenon; also shows ECG evidence of right ventricular strain but no clinical failure as yet
12. E. K.	11/21/46 12/17/45 1/15/46	15 13 ..	24 19 ..	16 13 8	24 19 9½	V.P.'s generally elevated and P-R consistently positive; ECG showed evidence of infarct; thoracoplasty contraindicated by heart condition
13. I. K.	10/21/46	7	6½	8	8	V.P.'s normal; died of massive hemorrhage; autopsy revealed normal heart
14. J. K.	6/ 5/47	6½	6½	5½	5	V.P.'s normal; severe emphysema but no cardiac insufficiency
15. A. K.	4/23/47	12½	16	Elevated V.P. and positive P-R; has gone on to severe decompensation
16. M. L.	5/19/47	4½	4	Normal V.P.; severe dyspnea due to pulmonary destruction and emphysema
17. G. L.	4/23/47	4	4	3½	3½	Normal V.P.'s; dyspnea due to extraperiosteal thoracoplasty on the left and disseminated disease
18. E. M.	5/ 9/47	10½	10½	9	9	V.P.'s upper normal; developed evidence of right heart failure on the surgical table and pulmonary resection could not be completed; subsequent rapid infusion test showed latent cardiac insufficiency
19. A. M.	3/24/47	3	4	5	6½	An instance of frank right heart failure due to thyrotoxicosis, with auricular flutter and fibrillation, and with normal initial V.P.'s but positive P-R phenomenon
20. P. M.	7/31/46 8/ 1/46 8/ 2/46 8/ 7/46	10 12 10 6	12 18 12 10½	19 16½ 19 10	22½ 23 22½ 14½	Elevated V.P.'s; positive P-R phenomenon; admitted in congestive failure and died 9/7/46
21. H. M.	8/21/46 10/16/46	8 21	8 28	9 21	9 30	Normal V.P.'s on admission; later elevated with positive P-R; died 10/18/46; autopsy revealed hypertrophy and dilatation of the right ventricle
22. M. O.	4/ 8/46	8	6½	7½	6½	Normal V.P.'s; severe dyspnea due to thoracoplasty on left, emphysema on right
23. T. R.	3/21/46 3/26/47	6 ..	6 ..	10 14	10 18	Admission V.P.'s normal; later elevated with positive P-R; clinical evidence of right heart failure appeared on 3/29/47; died 3/31/47
24. P. S.	3/20/46	4	4	6	5½	Normal V.P.'s; very severe dyspnea due to disseminated disease
25. R. S.	2/11/46	9	10½	4½	5	Normal V.P.'s; positive P-R dyspnea due at least to other evidence of cardiac observation
26. M. S.	2/11/46 5/20/46 7/17/46	9 19 ..	10½ 24 ..	4½ 17½ 17	5 24 24	V.P.'s normal to elevated; P-R always positive; died of massive hemorrhage 10/14/46; autopsy revealed right ventricular hypertrophy and dilatation
27. F. W.	9/5/46 9/14/46	4½ 5½	4½ 5½	4½ 8½	4½ 8½	Normal V.P.'s; dyspnea due to extensive parenchymal destruction; although a desperately poor risk, has withstood 5 major operations
28. C. W.	4/11/46 5/18/47	17 ..	22½ ..	18 8½	23 11	Elevated V.P.'s and positive P-R; dyspnea due to cardiac insufficiency on basis of thoracoplasty and disseminated diseases
29. E. W.	12/27/46	15	15	15	15	Elevated V.P.'s; no P-R; A-L time normal; A-T time prolonged; diagnosis: arteriosclerotic heart disease; left ventricular insufficiency
30. G. W.	2/ 4/46	8	6½	7	7	Normal V.P.'s; very severe dyspnea due to left extraperiosteal thoracoplasty and extensive disease

* Venous pressures are recorded to the nearest half-centimeter.

† The upper limit of our apparatus.

instances of emphysema without heart failure, in which the venous pressure was somewhat elevated, but in the majority the pressures were within normal limits. In our experience, emphysema *per se*, in the absence of right ventricular insufficiency, does not cause elevated venous pressure.

Nemet and Rosenblatt¹¹ reported an incidence of right ventricular hypertrophy of 46.5% in 71 consecutive cases of pulmonary tuberculosis coming to necropsy. "While it is true," they state, "that *cardiac enlargement* and *cardiac failure* are by no means synonymous terms, nevertheless the former represents an earlier phase of the latter condition. It seems rational, therefore, that, just as there is a transition period of pathologic changes, there should be a transition period before the patient goes into recognizable cardiac failure in which the cardiac symptoms are obscured by those of the pulmonary disease. At present it is impossible to distinguish clinically between pulmonary and cardiac insufficiency in the early stages of cardiac failure." Actually, only 11 of their 33 cases were recognized clinically (antemortem) as having heart disease. Less than half showed hepatomegaly or peripheral edema. Roentgenograms and electrocardiograms were of scant value in establishing the cardiac diagnosis, and "venous pressure readings did not always parallel the degree of venous distention." Hitzig⁸ also pointed out this occasional failure of the conventional venous pressure determination to indicate even frank cardiac insufficiency. An example in our

own series may be seen in Case 19. It will be noted however that the positive Pasteur-Rondot phenomenon is present in that instance. We feel that use of this test in addition to the usual venous pressure determination offers a reliable and quite sensitive index of the functional reserve of the right heart.

Final proof of this last statement must await accumulation of a considerable series of autopsy cases. Of the 30 cases in Table 2, 7 have so far died, and of these, 4 have come to autopsy. Of the latter, 3 had antemortem elevated venous pressures and positive Pasteur-Rondot phenomenon and showed postmortem evidence of cardiac failure. One who showed no postmortem evidence of failure had normal venous pressures and a negative Pasteur-Rondot response in life (Case 8).

Conclusions. 1. Venous pressure studies on 55 patients with pulmonary tuberculosis confirm earlier reports that changes in the venous pressure are inconstant, often transient, and usually unilateral on the side of more extensive disease or collapse.

2. Peripheral venous pressure bears a linear relationship to positive intrathoracic pressure but probably not to negative intrathoracic pressure.

3. Venous pressure determination, if use is made of the hepatojugular reflux phenomenon of Pasteur and Rondot, offers a valuable means of detecting cardiac insufficiency in cases where cardiac symptoms may be obscured by concurrent pulmonary disease.

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PAIN REACTION THRESHOLDS IN PSYCHONEUROTIC PATIENTS*

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THE diagnosis of psychoneurotic states is too frequently made on the basis of exclusion. A clinically applicable diagnostic test to aid in the confirmation of such a diagnosis would be of considerable value, especially on the medical and surgical wards of a general hospital where the services of a psychiatrist may of necessity be limited to those patients who are obviously mentally ill. Chapman¹ and Chapman *et al.*^{2,3} have reported that psychoneurotic patients, including those with anxiety tension states, conversion hysteria, and hypochondriasis have a lower pain reaction threshold than do the non-neurotic controls, and they suggest that "this test might be used as an aid in the diagnosis of neurocirculatory asthenia, effort syndrome, and anxiety neurosis."² An experiment of ours in progress at the time of publication of their report was designed to investigate the feasibility of using the Hardy-Wolff-Goodell pain threshold apparatus as a diagnostic aid in an unselected series of general medical patients.

Materials and Method. The Hardy-Wolff-Goodell apparatus⁴ was modified so that light from a 500 watt incandescent lamp passing through a condensing lens was focused through a fixed aperture onto the blackened skin of the subject's forehead and hand alternately. The sites selected for testing were the midline of the forehead and the dorsum of one hand on each subject. An electrically timed shutter was opened for exactly 3 seconds for each trial. A complete test for one subject included a series of 8 to 15 different stimuli of varying strengths so administered as to allow the determination

of the pain perception threshold and the pain reaction threshold, the lowest level from either the forehead or the hand being considered as the threshold.

The pain perception threshold is the lowest level of stimulation at which the subject perceives a sharp, stinging, prickling sensation. The pain reaction threshold is the lowest level at which the subject demonstrates a motor reaction, that is, a wince or a withdrawal.

A voltmeter was attached across the lamp circuit, and the instrument was calibrated so that the amount of radiant energy passing through the testing orifice at any particular voltage was known accurately. This calibration was checked frequently, and it was found that the energy output for a constant voltage was constant from day to day.

Prior to testing, subjects were instructed as to the nature of the endpoint for perception by being told that sometime during the series of trials they would feel a sharp, stinging, burning, jabbing, pricking, prickling sensation or they would feel as if the warmth swelled to a point at the end. They were told that the sensation of warmth was not the desired endpoint. Reaction was not mentioned before the test.

Unselected ambulatory patients from the medical wards of the State of Wisconsin General Hospital were tested within a few days of their admission. Clinical studies and diagnoses were not available to the operator until each test had been completed. The diagnoses were then recorded together with the pain perception and pain reaction thresholds. All tests were performed by the same operator. None of the patients had received analgesics on the day of the test.

The subjects were divided into two groups for statistical analysis: (a) 71 patients with a primary diagnosis of psychoneurosis. This

* Aided by a grant from the Wisconsin Alumni Research Foundation.

group was predominantly composed of patients with anxiety tension states but included some patients with conversion hysteria or hypochondriasis. A few of them also had organic disease which was not considered to be detrimental to the validity of this test. (b) 138 non-neurotic subjects, including 108 non-neurotic medical patients and 30 medical students and hospital personnel.

Results. The pain *perception* threshold proved to be a mean for 138 non-neurotics of .348 gm.cal./sec./cm.²* and a mean for 71 psychoneurotics of .347 gm.cal./sec./cm.² This is not a significant difference in the means.

The pain *reaction* threshold showed a mean for 138 non-neurotics of .502 gm.cal./sec./cm.² and a mean for 71 psychoneurotics of .447 gm.cal./sec./cm.²

This is a highly significant difference between the two means; the critical ratio is over 4.9, indicating that these results would occur by chance less than once in 10,000 trials.

Discussion. The diagnosis of psychoneurosis were made by the medical staff. Over 50 % of the psychoneurotic patients were examined by a psychiatrist who confirmed the diagnosis.

The difference between the mean pain *perception* threshold of psychoneurotics and that of non-neurotics is not significant statistically. There is practically no difference between the means. This is in direct contrast to a widespread but very likely erroneous clinical impression that psychoneurotics feel pain from a lesser stimulus than do non-neurotics.

The difference between the mean pain *reaction* threshold of neurotics and non-neurotics is highly significant statistically. Inspection of the graph (Fig. 1), which compares the pain reaction threshold of psychoneurotics and non-neurotics, reveals that, despite a highly significant difference in the mean reaction thresholds, there is extensive over-lapping of individual levels in the two groups. It is apparent that there is no demarcation which might serve as a dividing line in clinical application of

this test. Fifty-two per cent of the psychoneurotic group had a reaction threshold below .455 gm.cal./sec./cm.² while only 23 % of the non-neurotics reacted below this level. Using .385 gm.cal./sec./cm.² as an arbitrary point of differentiation, one finds 30 % of the psychoneurotic group reacting below this level, while only 6.5 % of the non-neurotic group had a pain reaction threshold below that figure.

Psychoneurotics are more apt than non-neurotics to demonstrate a fusion of their perception and reaction thresholds; that is, to react as soon as they perceive pain. Of the psychoneurotics, 18.3 % fused their perception and reaction, while only 4.3 % of the non-neurotics exhibited this phenomenon. It is of interest to note the nature of the illnesses in the 4.3 % of the non-neurotic group who had no spread between perception and reaction thresholds. There were 7 subjects in this group. The 2 men had peptic ulcers. One of the 5 women was later diagnosed as probable conversion hysteria; 1 had a duodenal ulcer; 1 was a behavior problem and had syphilis; 1 had a spontaneous pneumothorax; and 1 was a medical student with no known disease.

The fact that each subject was tested only once might be considered by some as detracting from the validity of the results. This criticism was anticipated, but the experiment was designed to determine the feasibility of using this apparatus as a clinical aid in the diagnosis of psychoneurotic states. Because of this goal it was considered advisable to test each subject only once. The method would be less practical for clinical use if it were necessary to test each subject on several different days. Chapman *et al.*² have shown that 11 subjects tested on 6 consecutive days failed to show any significant variation from the value recorded on the first test.

Reference to the graph (Fig. 1) reveals that many of the subjects clinically diagnosed as psychoneurotics had a pain reaction threshold as high as that of the non-

* Gram calories per second per square centimeter.

neurotics. It is also apparent that a not inconsiderable number of non-neurotics had a low pain reaction threshold. There were numerous cases in which the clinical diagnosis of several independent examiners was anxiety tension state, although the pain thresholds of these same subjects were definitely in the higher levels. Stated differently, these psychoneurotics had "normal" pain reaction thresholds.

pain reaction thresholds and pain perception thresholds were determined in 71 patients with a diagnosis of psychoneurosis, and in 138 non-neurotic patients and medical personnel.

There was no significant difference between the mean pain *perception* threshold of psychoneurotics and non-neurotics.

There was a highly significant difference between the mean pain *reaction* threshold

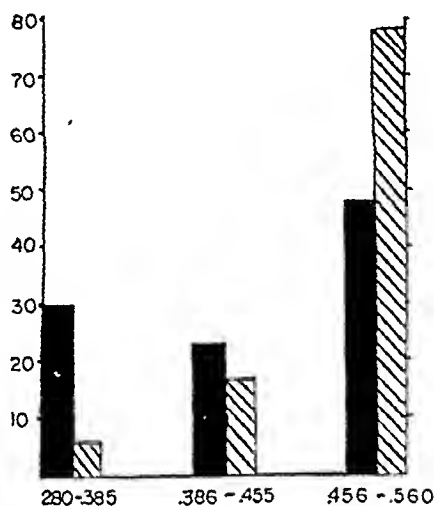


FIG. 1.—Pain Reaction Thresholds. Solid: Psychoneurotics. Diagonal: Non-neurotics. Abscissa: Pain reaction threshold expressed in gm.cals./sec./cm.² Ordinate: Percentage of subjects reacting between these levels.

It is realized that the patients diagnosed as psychoneurotics form a very heterogeneous group. Even those with an anxiety tension state are a heterogeneous aggregation, and one might anticipate considerable scattering of the pain thresholds in a group of psychoneurotics, or even in the more limited classification of anxiety tension state. However, it is apparent that a considerable number of psychoneurotics have a definitely low pain reaction threshold. From results obtained in this experiment, the authors were unable to establish the common factor necessary for manifestation of a low pain reaction threshold.

Summary and Conclusions. 1. Using a modified Hardy-Wolff-Goodell apparatus,

of psychoneurotics and non-neurotics, that of the neurotics being distinctly lower.

2. Failure to show a spread between perception and reaction threshold is strong evidence for the existence of a significant emotional disturbance. It occurs more often in psychoneurotics than in non-neurotic persons. However, a normal pain reaction threshold is not evidence against the existence of a psychoneurosis, since a considerable number of severe psychoneurotics showed normal pain reaction thresholds.

3. The Hardy-Wolff-Goodell pain threshold apparatus is of limited value in confirming the diagnosis of psychoneurosis, but of no aid in ruling out such a diagnosis.

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A VASCULAR APPROACH TO THE TREATMENT OF RHEUMATOID ARTHRITIS*

A PRELIMINARY REPORT

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THE present concept of the etiology, pathology and treatment of rheumatoid arthritis is at best an inconclusive, individualized interpretation of a mass of conflicting clinical and laboratory data. As with few other diseases, speculation has run the gamut experimentally and therapeutically, and one needs only to read the pertinent literature to direct accordingly his approach to the patient's disease. Comroe,⁴ in his monograph on arthritis, has exhaustively compended this maze of statistical conflict.

In the literature, both old and new, there are many references to the abnormal vascular pattern of rheumatoid arthritis. Few authors have presented any sound evidence of this suspected vascular alteration. Considerable investigation, however, has been carried out in the therapeutic effect on the disease by agents tending to alter or correct the vascular picture.^{5,14,20,21} Some workers have failed to demonstrate any vascular change and, therefore, have questioned its existence or have assumed that, if present, it represents nothing more than a concurrent feature.^{1,9,21}

Recently there have appeared in the literature a number of valuable presentations which may lead to a clearer understanding of the basic vascular condition in rheumatoid arthritis. Pemberton and Wright,²² and Kovacs, Wright and Duryce,¹³ a number of years back, attempted to illustrate vascular changes by the measurement of the temperature of the nail-beds in arthritic individuals. More

recently Martin *et al.*,¹⁵ by careful evaluation of skin temperatures, demonstrated a sluggish vasoconstriction and vasodilatation in many subjects with rheumatoid arthritis.

Kersley,¹² in a series of cases, reported vasospasm as an early feature of this disease. Naide *et al.*,¹⁶ felt that vasospasm might well be a predisposing factor, and further stated that the individual with rheumatoid arthritis has a high degree of vascular tone which they defined as an impairment of the lability of the blood vessels. The characteristic pattern which they felt diagnostically important was the persistently high grade of vascular tone with a dissociation type of response in the involved digit or extremity. This concept of a characteristic vascular pattern in rheumatoid arthritis is in contrast to that of Hench,⁹ who ascribed the vasomotor changes of chronic arthritis as neither the cause nor an essential feature of the disease, but rather as a complication occurring at times in varying degrees as the sympathetic nervous system was perhaps affected by "toxins" of the disease.

Naide *et al.*,¹⁶ felt that there was evidence presented by patients with rheumatoid arthritis suggesting an increased sympathetic tone which accounted for the high vascular tonicity as well as many other features, such as increased sweating and increased pupil size. This evidence of autonomic nervous system imbalance in rheumatoid arthritis gives rise to interesting speculation as to the rôle of the auto-

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nomic nervous system in rheumatoid arthritis in relation not only to etiology but to treatment.

Many of the accepted and commonly used therapeutic agents basically are vascular in effect, and many others not of this specific nature may quite likely exert such an effect. The efficiency of certain of these standard agents, from a vascular standpoint, has been repeatedly reported. The use of massage and heat of various forms has long been associated with the handling of rheumatoid arthritis. Woodmansey²¹ describes the vascular reactions to contrast baths and states that the effect sought is the active exercise of the peripheral vessels. Sympathectomy has been shown to improve circulation in peripheral joints and to relieve joint pains.^{5,17} Ganglionectomy is occasionally used to relieve pain in rheumatoid patients, the benefits resulting probably from improvement in local circulation by the blocking of sympathetic outflow.²⁰ Naide¹⁶ suggested that treatment such as that given in other vasospastic disorders, in which emphasis is directed towards vasodilatation by interruption of hyperactive vasoconstrictor reflexes through paravertebral block or caudal anesthesia might benefit these patients. Artificial fever therapy has been shown to produce partial symptomatic relief of days or weeks duration.^{3,19,20} Martin *et al.*,¹⁵ by vasodilatation using physiotherapeutic measures, showed that after 7 to 30 days of treatment patients showed an increased tolerance to cool environmental temperatures. The use of large doses of nicotinic acid, both intravenously and orally, for its vasodilating effect has been reported by Kurtz¹⁴ who in treating 36 cases, mostly chronic and of long duration, obtained favorable results with improvement in almost 75 %.

In 1946, Gillman and Gillman⁷ reported favorable results obtained with 70 patients who had polyarthritis, using an unorthodox spinal pumping procedure first described by Speransky.¹⁸ They noted objective and subjective signs of improvement within 48 to 72 hours in more than 80 %

of their cases. Unfortunately in the reporting of these cases, no attempt was made to subclassify these arthritides, so that proper evaluation of the reported results is difficult. The remarkable feature, however, was the profound effect of the pumping procedure on the peripheral vascular mechanism as evidenced by severe sweating, a rise in skin temperature, and a marked dilatation of capillaries. The degree and duration of the dilatation of the peripheral vessels was much greater than that achieved by sympathetic blocks, according to the authors. This effect was maintained in many patients for months.

Gubner⁸ noted an increase in peripheral blood flow by the use of amino acids, notably glycine. He reported the effects in 25 patients, 9 of whom had peripheral vascular diseases. The method was not used in patients with rheumatoid arthritis. He found that the skin temperature rises obtained were fully equivalent to those resulting from nerve block, indicating maximal vasodilatation.

THERAPEUTIC METHODS. An approach to the management of rheumatoid arthritis mainly from a vascular viewpoint appeared to be worthy of consideration. The treatment that has evolved at this Naval Hospital consists of agents and procedures for influencing the vascular system.

Upon admission of a patient with acute involvement of joints, constant packing of both the involved joints and the surrounding soft tissue well beyond the involved joints is initiated immediately, using hot moist foment. This is continued for a period of 72 hours or more until the acute edema and the acute pain have been alleviated or eliminated. The packing is similar in technique to that described by Kenny.¹¹ Following this phase, the patient is then subjected to the spinal flushing procedure of Speransky. The technique for this latter is that of doing first a lumbar puncture and then aspirating and reinjecting spinal fluid. Twenty cc. of spinal fluid are aspirated slowly consuming about 60 seconds; the fluid is then reinjected at about the same rate without

removal of the syringe or needle. This is repeated 20 times. The final 20 cc. of fluid withdrawn is not re-injected but is sent then to the laboratory for routine spinal fluid analysis. Further treatment is then withheld for the next few days until all deleterious effects (mainly headache) secondary to the spinal pumping have disappeared.

The patient then begins a course of typhoid vaccine-autohemotherapy. The course consists usually of 6 fever sessions induced twice weekly for 3 weeks. At the same time that triple typhoid vaccine is given intravenously, 10 cc. of the patient's blood withdrawn from the arm are re-injected into the gluteal muscles. A violent chill with subsequent fever of 102 to 104 degrees sustained for 4 to 6 hours is the effect desired.

Between these fever treatments the patient is given nicotinic acid orally twice daily before meals in amounts sufficient to produce peripheral flushing.

Diets consist of normal house diets containing approximately 2200 calories.

Physical therapy is utilized in those cases where indicated. Remedial exercises and reambulation are initiated early by the Physical Medicine Department.

In the process of the evolution of this current method of handling rheumatoid arthritics, many patients received trials with only spinal pumping or with only fever therapy before the combined use of spinal pumping and typhoid-autohemotherapy was found to be productive of the best results.

Results of Treatment. In 11 patients of this series, active treatment consisted of Speransky spinal pumping alone. Nine of these patients were clearcut cases of rheumatoid arthritis, 1 of Marie-Strümpell arthritis, and 1 of psoriatic arthritis. Except in the case of psoriatic arthritis and that of Marie-Strümpell arthritis, there were certain definite subjective and objective benefits obtained in all cases. The most consistent effect was the marked decrease or elimination of the annoying fibrositic component complained of by the

patients; not only was there improvement in the jelling experienced with waking in the morning but also with the jelling secondary to inactivity and that associated with barometric changes. Secondary to this improvement, the patient's sleep improved, his appetite increased, he felt well in the morning, and his general sense of well-being was appreciably stimulated. In all cases there was some degree of improvement and in some, complete elimination of the peripheral coldness of extremities. Objectively, there was improvement in skin warmth and a decrease in blueness; while facilities were not available for reliably recording skin temperature changes in a constant temperature environment, the changes were nonetheless sufficiently marked both subjectively and objectively to be of striking significance. In general, there was diminution of joint pain but this was not a consistent observation. In contrast to the report of Gillman and Gillman⁷ who noted improvement in the acutely inflamed joints within 48 hours, there were no such changes noted in these patients, nor was there any consistent or significant change in sedimentation rates secondary to the pumping as reported by those investigators. Repumping was carried out in 3 cases; in 1 patient, who had experienced excellent effects initially with recurrence of symptoms after 44 days, repumping was again effective. In the 2d case repumping was carried out 3 months after the initial procedure because of poor response, and results following this 2d pumping were equally disappointing. In the 3d case there had been no complaints of coldness, jelling or other vasomotor symptoms. Pumping initially did not relieve joint pain, swelling or immobility, and a repumping 4 months later was similarly ineffective. In all cases except these 3 the beneficial effects obtained were sustained. In no cases were there ill effects other than the transient headaches secondary to usual lumbar puncture. Four cases of this group, of which 3 were the failures mentioned above, were later subjected to typhoid-autohemotherapy treatment.

Case Reports. **CASE 1.** W. D., a 24 year old white male admitted on April 22, 1946, had been chronically ill with rheumatoid arthritis for 5 years prior to admission. He had received gold therapy with no effect. The year before admission he had been placed in a hip spica cast to prevent joint deformity of the left hip; ankylosis of the left hip and of the lumbar spine resulted. Serial Roentgen ray studies have shown a progressing fibrous ankylosis of the left hip and spine with roughening of the left femoral head and decrease in joint space, progressive bridging of the intervertebral spaces of the lumbar spine, obliteration of the sacro-iliacs bilaterally, and beginning changes in the inferior portion of the right hip joint. Readmission at this time was necessitated by dependent erythema and paresthesia of the left foot, and severe muscle cramping in the left leg. The latter was of such severity that the patient was bedridden, afraid of moving for fear of precipitating such episodes. During the entire period of illness the patient had an elevation of his sedimentation rate. On conservative measures of bed rest and blood transfusions, there was no response clinically.

On July 15th he was given a Sперansky spinal flushing. As a result there was immediate increase in warmth of extremities, elimination of jelling, and relief of the leg spasms. The sedimentation rate remained elevated. Nine days following the pumping, the patient was sufficiently free of pain to begin walking in a mechanical walker.

On September 5th because of lack of increase in motion in the deformed joints, it was decided to have the left hip and knee manipulated. As a trial to determine the efficacy of increased blood supply in such a procedure it was decided to repump; this was done on the 5th and the following day manipulation under intravenous anesthesia was carried out. Despite traction, underwater exercises, and physiotherapeutic measures, the motion gained by manipulation was lost, the patient was not benefited, and apparent ankylosis returned.

On October 10th, because of hip joint pain and in order to ascertain the rôle of joint pain in the limitation of joint motion, paravertebral blocks were carried out on 2 occasions; for 2 hours after the 1st block the patient was able to accomplish some painless hip motion, but the subsequent block was a failure.

On November 20, 1946, the sedimentation rate was for the first time normal.

On January 16, 1947, a vitallium cup arthroplasty of the left hip was performed. To date, results have been good; the patient now has good range in all directions except hypertension of the hip (this limitation being largely due to low back ankylosis). The sedimentation rate has remained normal.

Since the initial Sперansky the subjective warmth and comfort in the affected parts has remained good; the relief from jelling has persisted.

CASE 2. W. W. P., a 30 year old white male, admitted on March 16, 1946, had chronic rheumatoid arthritis with advanced deformities of the small joints of both hands and feet and marked generalized muscular atrophy.

In the summer of 1943 the patient had noticed a painful right ankle for one week. In August, 1944, he developed pain and stiffness in the left knee, which improved under symptomatic treatment. In October, 1944, he developed acute pain and swelling in the right ankle and was then hospitalized by the Army. While in the hospital there was progressive spread, with involvement of the elbows, wrists, fingers, knees, ankles and feet. There was increased local heat and swelling, most marked about the knees, and limitation of motion in both hips. In the first 2 months of his illness he lost 70 pounds in weight, from a normal of 160 pounds to 90 pounds. He was treated with physical therapy and general supportive measures. Following transfer to the United States he was given a course of gold (775 mg.) with no subjective benefit; physiotherapeutic measures were continued.

Upon admission to this hospital in March, 1946, 3 years after the onset, the patient weighed 100 pounds. There was marked generalized muscular atrophy, pain, swelling and contracture deformities of the elbows, wrists, fingers, knees and feet. The blood sedimentation rate was 27 mm. in 1 hour. It was felt that he had an extensive deforming arthritis which was still in an active stage. He was treated for the first 3 months with blood transfusions, prostigmine, physical therapy and general supportive measures. There was no improvement.

On July 29, 1946, a Sперansky spinal flushing was done. On the first day following this procedure the patient noted subjective

warmth of the hands and feet and diminution of pain upon joint motion. Objectively there was marked increase in cutaneous warmth. The patient no longer had jelling; slept well and felt well upon awaking in the morning. There was a general increase in sense of well-being and an increase in appetite. By the 7th day the patient felt that joint movements were freer and he began walking with mechanical aids. Fifty-five days after the pumping the patient was started on a 200 gm. protein diet supplemented by intravenous protein feeding. Physiotherapeutic and general supportive measures were continued. On a graduated activity program he became reambulated. One hundred and thirty-eight days following the pumping the initially noted beneficial effects were still present. Upon discharge in February, 1947, he had regained 34 pounds, was ambulatory, and was retaining his Speransky effects.

TYPHOID VACCINE-AUTOHEMOTHERAPY ALONE. Three patients with clear-cut rheumatoid arthritis were treated with typhoid vaccine-autohemotherapy alone. In all of these patients there was elimination of joint pain, a marked decrease in joint swelling, and an increase in joint mobility usefulness. Following a depression of appetite during the febrile state, there was considerable improvement in appetite following the treatment. There was no effect on the jelling or other changes in the vasomotor manifestations of the disease. The sedimentation rates showed no decrease and in some cases showed an increase. There were no ill effects.

CASE 3. Mrs. H. B., a 24 year old white female, admitted on December 2, 1946, had typical spindling of the proximal interphalangeal joint of the left second finger, enlarged and tender second metacarpophalangeal joints bilaterally, enlargement and limitation of range of motion in the right wrist, and tenderness of the small joints of both feet. There had been no weight loss. The blood sedimentation rate was 30 mm. in 1 hour and there was no anemia.

The onset of the illness had been 3 years previously, following the birth of a second child. Initially there had been acute swelling and soreness of the small joints of the feet with associated periarticular redness and

tenderness and migration to involve the fingers, wrists, knees and shoulders. In the course of the 3 years prior to admission, the patient had been variously treated by 15 doctors without appreciable benefit.

After admission to this hospital, the patient received a course of 6 fever treatments with typhoid vaccine and blood with good febrile responses. Thirteen days after admission she was discharged with objective and subjective improvement; final evaluation was withheld until she had returned to full activity. Upon discharge the patient was given nicotinic acid to be taken in 200 mg. doses (taken in 2 doses of 100 mg. each at 15 minute intervals) twice daily before the noon and night meal for its cutaneous flushing effect. A recheck 1 month following discharge from the hospital revealed no joint symptoms except for residual periarticular thickening about the right wrist and tenderness about the small joints of the right foot. There was increased range of motion in the right wrist, and all metacarpophalangeal tenderness and joint limitation had subsided. There had been slight improvement in jelling. However, there had been only a slight change in the other subjective peripheral vasomotor complaints, and the jelling with barometric changes which previously had been a major complaint persisted in some degree, in spite of the fever sessions and the nicotinic acid flushes.

COMBINED SPERANSKY AND FEVER THERAPY. Seventeen patients were treated with a combination of Speransky spinal pumping and typhoid vaccine-autohemotherapy. Of this group, 14 were clear-cut cases of rheumatoid arthritis and 2 were arthritides probably of the rheumatoid type.

The patient with Maric-Strümpell arthritis received no benefit from either the Speransky procedure or from the course of typhoid vaccine-autohemotherapy.

Of the 2 probable rheumatoid cases, 1, an intermittent hydroarthrosis case, received moderate benefit from the spinal pumping and was considerably improved following the 6 fever treatments. The second probable rheumatoid patient obtained marked improvement in his vasomotor and fibrositic symptoms from the

spinal pumping, and in the course of his typhoid vaccine-autohemotherapy his joint manifestations subsided completely so that he could be promptly discharged from the hospital.

Of the remaining 14 patients, 4 had been treated initially with spinal pumping alone and required additional therapy. Of these 4, one remained only slightly improved following the use of typhoid vaccine-autohemotherapy, while the other 3 promptly went into remission.

Of the 14 true rheumatoid arthritics receiving the combined treatment, 2 felt that the spinal pumping had been of no benefit, 4 felt only slight improvement, 6 were moderately improved, and the remaining 2 were markedly improved. On the other hand, of this same group, 5 felt that the additional typhoid vaccine-autohemotherapy was of maximum benefit, 6 felt it of marked benefit, 3 were moderately improved and in only 1 case was the response of slight or doubtful value. This latter patient was the same who had received minimal benefit from the spinal pumping.

The subjective and objective results from the use of the combined treatment were those described for the Speransky pumping and the fever when used singly. There was no consistent effect on the sedimentation rate of the blood.

In 2 of the cases so treated, the immediate beneficial results were not sustained, and there was a subsequent recurrence of activity. These patients are currently still hospitalized and they have not yet received further pumping or fever, so that the ultimate prognosis is still questionable.

The average age of the patient in this group was 42 years; the average duration of his arthritis 20 months.

CASE 4. C. F. P., a 56 year old white male admitted on January 25, 1946, was in a primary attack of rheumatoid arthritis involving the knees, hands, and fingers. There was a progression with involvement additionally of the knees, ankles, and shoulders, so that the patient became bed fast. He was variously treated with chrysotherapy

(1000 mg.), numerous physiotherapeutic modalities, prostigmine, and general supportive measures, but with persistently unfavorable progress.

In July, 1946, he was discharged unimproved. When readmitted to the present arthritic service in August, 1946, he was experiencing such severe joint pain that he could not move. There was enlargement and tenderness of both knees with marked quadriceps wasting, enlargement and moderate tenderness of the proximal interphalangeal and the metacarpo-phalangeal joints bilaterally, enlargement and moderate tenderness about the wrists and elbows and adduction contractures of both shoulders. The blood sedimentation rate was 30 mm. in 1 hour.

On August 15, 1946, the patient was given a Speransky spinal flushing without adverse effects. Two days later he reported subjective decrease in joint pain and improvement in joint mobility. By the 4th day there was no residual pain or joint distress; objectively there appeared to be increased joint motion. On the 6th day the patient walked with support and by the 12th was walking on crutches to the Ship Service store. By the 17th day he was getting in and out of the bathtub without support. By the 44th day after the pumping there was some beginning return of joint stiffness in the hands and by the 65th day there was appreciable return of arthralgic symptoms. These latter persisted and increased so that on the 75th day following the initial Speransky treatment the patient was given a 2d spinal flushing, and again there was beneficial response. The patient noted then that he could lie on either side and could sleep with his arms under his pillow. On the 115th day a course of typhoid vaccine-autohemotherapy treatments was initiated; over the next month 6 good febrile responses were induced. On January 21, 1947, the patient received a 3d spinal flushing, and on January 27, 1947, 5½ months following readmission, he was discharged from the hospital. In the course of his stay in the hospital the patient received general supportive therapy, including high protein feeding, accessory intravenous Amigen and plasma therapy, local Roentgen ray therapy to the periarticular thickening and edema about the carpo-metacarpal joints of both hands, physical therapy, and a graduated exercise-activity program. Upon discharge

he was symptomatically quiescent and ambulatory. The sedimentation rate remained static, 26 to 30 mm. in 1 hour throughout the hospital stay.

CASE 5. R. V. B., a 56 year old white male admitted on September 4, 1946, came to the hospital in a wheelchair. He was unable to stand and had to be lifted from the chair to his bed. There was marked swelling, tenderness and increased local heat about the right wrist, the first metacarpophalangeal joint, the right elbow, both knees, and both ankles. There was marked muscle wasting about the involved joints and the patient reported a weight loss of 45 pounds in the preceding 4 months. The sedimentation rate on admission was 26 mm. in 1 hour and there was an anemia, with 3.6 million red cells per c.mm., and 9 gm. of hemoglobin.

In May, 1946, 4 months prior to admission, the patient had developed acute tenderness and swelling of the left second toe with progression to the right knee and later to the left knee, the right hand, the right elbow, the right wrist and shoulder, and both ankles. He had received no treatment for his arthritis prior to admission.

On September 28th the patient was given a Speransky spinal pumping. For several days there was subjective decrease in joint pain and increased joint mobility but this was quickly transient, and, in retrospect, it was not considered significant. On October 29th a course of chrysotherapy was begun and a total of 500 mg. (Myochrysine) was given with no subjective or objective improvement. On January 13, 1947, the patient was given a spinal flushing and again there was no significant effect. On January 14, 1947, typhoid vaccine-autohemotherapy was begun and in the course of the next month the patient received 6 sessions with good febrile responses to each. Following the 3d fever, joint pain had markedly decreased and joint mobility had appreciably increased, so that the patient was able to begin stand balance exercise preparatory to reambulation. With each subsequent fever session there was marked improvement. There was improvement in appetite, general sense of well-being, and increase in weight. The patient was graduated to more and more active exercises in the remedial exercise gymnasium. Three months following initiation of the typhoid vaccine-autohemotherapy regimen the patient was ambulatory; he had

regained muscle bulk and muscle strength and 20 pounds of weight. There was residual slight heat and swelling about the left ankle and slight non-tender swelling about the right first metacarpal head. In the course of his management the patient had received a trial of prostigmine with minimal benefits; he had received intramuscular liver and oral iron preparations for his anemia, general supportive measures, and daily physical therapy. During the course of treatment the sedimentation rate has remained 26 to 30 mm. in 1 hour.

Discussion. The attempt to treat rheumatoid arthritis from a vascular approach is presented because of the definite effect produced in a relatively short period of time on an otherwise progressive disease. Nine patients demonstrating true rheumatoid arthritis were treated with spinal pumping alone. One patient with psoriatic arthritis and one with Marie-Strümpell arthritis were also subjected to this procedure.

It is difficult to postulate the mechanism of the action of the Speransky procedure. In his interpretation of disease, Speransky¹⁸ begins with the assumption that all disease represents an alteration in the general physiology of the body so that a new entity, or being, is produced. This, he reasons, is mediated through the nervous system; spinal pumping under such circumstances, he theorizes, produces an irritation of the nervous system and thus alteration of the pathologic nerve pathways and patterns, and production of new pathways and patterns. No attempt is made here to explain or theorize on the physiologic basis for the effects of spinal pumping, but rather to present the results obtained in this small series.

The patients treated in this series constituted a group that could be seen daily, living in a service hospital. All patients had had their disease for a long enough period of time to be classified as chronic cases; the duration of the disease in the patients receiving the pumping alone ranged from 1 to 22 years. The average age of the patients was 34 years. With the

exception of the case with psoriatic arthritis and that with Marie-Strümpell arthritis, all patients had received some standard forms of therapy, including chrysotherapy, physical therapy, prostigmine, and others, and all had failed to demonstrate any evidence of impending remission. Of the 9 rheumatoid arthritides treated, 8 were complete bed patients. All of the patients demonstrated evidence of activity such as anemia, increased blood sedimentation rates, and active joint involvement. In these patients with frank rheumatoid arthritis the response to pumping occurred within 48 hours. The patients noticed increased warmth in their extremities, and the severity of the pain in joints decreased, so that the patients attempted to move previously fixed joints. This observation is similar to that of Gillman and Gillman.⁷ In 1 patient the crippling muscle spasms of the left leg were entirely eliminated and have not reappeared even with extensive exercise, orthopedic manipulation, and later hip arthroplasty; his response has persisted 9 months. In another patient (Case No. 2), similarly marked changes were noted and have persisted until the present, 9 months following the procedure. Objectively the increased peripheral temperature and the resultant increased desire to move joints were the most notable effects. In deformed joints of long standing, with or without Roentgen ray evidence of fibrous ankylosis, little to no change was noted in joint mobility. Because of pain diminution in joints, patients attempted to walk in many cases; this might easily be interpreted as an actual increase in joint mobility. In 1 patient with intermittent hydroarthrosis who was previously unable to get out of bed without considerable pain and resultant increase in joint effusion, a diminution in joint pain was noted following the pumping and he was soon walking about with the aid of crutches and later without any assistance. His joint effusion decreased with the increase in his joint motion; this would tend to support the opinion of Muller⁶ that intermittent pres-

sure such as is caused by the physiological function of the joint assists the nutrition of the joint structures, particularly the joint cartilages.

In their observations, Gillman and Gillman⁷ reported the disappearance of subcutaneous nodules following spinal pumping and increased benefits following a second pumping. In the cases reported here, no such results were noted and in none of the patients did there occur any alteration in pathologically fixed joints or greater boosts in peripheral temperatures following repeated pumpings. In those patients responding to pumping initially, the peripheral temperatures never returned to the previous status.

Five of the patients pumped developed severe headaches following the procedure; these persisted from 1 to 8 days and were the only ill effects noted.

The patient with psoriatic arthritis demonstrated no alteration in his deformities and no changes in his skin lesions. The patient with Marie-Strümpell arthritis similarly showed no improvement from the procedure.

About the same time as the above patients were being treated with Speransky spinal pumping alone and observed for results, the use of artificial fever and autohemotherapy, in a modification of the technique described by Ishmael,¹⁰ was initiated, and 3 patients with rheumatoid arthritis received this form of therapy alone. Best and Taylor² have excellently discussed the benefits derived from a body chill and the subsequent febrile response. The center for chills has been well localized in the posterior aspect of the hypothalamus but the effect and reason for a chill have never been adequately explained.

Dubois² has investigated the responses of the malarial individual and the normal individual to artificially induced chills and fevers; he demonstrated rapid elimination of extra heat in the normal and slow elimination in the malarial patient, the inference being that there apparently is a tendency toward retention of heat and subsequent prolonged vasodilatation in

the diseased individual. It is known that individuals repeatedly exposed to fever and chills develop a general step-up in their body metabolism, a fact attributed by some authors to thyroid stimulation. Best and Taylor² suggest that the elaboration of antibodies is facilitated and perhaps made possible only by high fevers. Ishmael¹⁰ states that while the effects of autohemotherapy are not clearly understood, one effect is apparent and that is desensitization.

Previous use by these authors of externally induced hyperthermia in the treatment of rheumatoid arthritis had been disappointing. Soloman and Stecher,¹⁹ and Martin¹⁵ have reported the therapeutic effect to be short-lived and of a palliative nature. It was therefore speculated that chilling might play an important rôle and that this together with the direct action of bacterial toxins upon the heat center or centers might effect a greater specific response and thus a better therapeutic effect for the patient. It was with this background that an attempt was made to observe the efficacy of combined typhoid vaccine-autohemotherapy in the management of rheumatoid arthritis.

Three patients were subjects to the typhoid vaccine and autohemotherapy; the results have been presented above. In 2 of these patients who showed evidence of remission of their arthritis, there persisted complaints which appeared to be some of those benefited by the spinal pumping procedure. Therefore, it was decided to combine these two approaches to treatment and observe the effects.

Seventeen patients were given the combined treatment of spinal pumping together with typhoid vaccine autohemotherapy. The results have been summarized previously in this article. During their chills the patients complained of rather severe pain particularly in their affected joints but during their febrile stages they experienced a feeling of well-being. Objective evidence of joint changes such as diminution in periarticular thickening, increase in joint motion, and, in some

patients, resorption of fluid in tendon sheaths became apparent after 4 or 5 treatments. In 1 patient who had had a spinal pumping and was receiving chrysotherapy, evidence of joint activity became apparent. He had received 500 mg. of gold thiosulphate at that time. It was decided to repeat the spinal pumping and start the fever regimen. After 3 sessions of typhoid vaccine-autohemotherapy fever, there was no objective evidence of residual joint activity; a total of 6 fever sessions were given and the patient's disease remained in remission.

The optimum febrile response desired was a temperature ranging from 102 to 104° and sustained for from 4 to 6 hours. Fevers of less degree or of shorter length appeared to be less effective in the patients' objective and subjective responses. In the course of 6 such bouts of fever, patients lost an average of 7 to 10 pounds in weight, but this was usually readily compensated for within 2 weeks following cessation of the fever sessions.

Frequently the fever curve showed 2 rises, the first attributable to the typhoid vaccine and the second, 3 to 4 hours following the chill, attributable to the absorption of the blood.

In the intervals between fever sessions, in order that they might experience as much comfort as possible, the patients were given nicotinic acid twice daily for its peripheral flushing effect. This was given twice daily on an empty stomach prior to the noon and evening meals in sufficient doses to produce subjective peripheral warmth. Doses of 200 mg. (100 mg. in 2 doses at 15 minute intervals) were usually adequate to produce the desired effect.

OTHER MEASURES. No effort has been made in this paper to elaborate upon the many supportive measures necessary in the overall handling of the arthritis. In brief, the use of chrysotherapy and prostigmine has been uniformly disappointing. The use of various detailed dietary regimens and extensive bed rest alone have been non-productive, and the latter grossly

detrimental and responsible for atonicity, atrophy, and contracture-deformities in muscles.

The use of physical therapy agents, including early remedial exercises and early reambulation training, together with occupational therapy, are important adjuncts to treatment and have been freely used. Braces are important for the prevention and the correction of deformities.

In several more debilitated patients the use of high protein (200 gm.) diets together with frequent supplementary intravenous Amigen and plasma feedings has given excellent results.

Roentgen ray therapy peripherally had been of no value in our cases. However, in cases of Marie-Strümpell arthritis Roentgen ray therapy, using the Freiberg technique, had been the most effective single agent in treatment.

More recently glycine orally and nicotinic acid orally have been used as supportive measures for their peripheral vascular effects. Conclusions cannot yet be drawn as to the relative merits of these substances, but the current impression is that the former is of little value because of the diarrhea and anorexia which frequently occur as side effects; nicotinic acid, on the other hand, in flush doses appears to be definitely of value in alleviating peripheral vasomotor symptoms.

Summary. 1. In 27 cases of chronic arthritis, treatment has been directed along a vascular approach to the disease. All cases were patients who had been chronically ill for 1 to 22 years and who had been unsuccessfully treated with the gamut of usual therapeutic measures.

2. In 1 case of psoriatic arthritis and 1 case of Marie-Strümpell arthritis, the use of Speransky spinal pumping was of no effect.

3. In 9 cases of clear-cut rheumatoid arthritis treated with Speransky pumping

alone there were immediate beneficial effects in 7 instances. In 1 case the response was minimal. In the remaining case there had been no subjective complaints of a fibrositic or vasomotor nature and in this patient there were no effects noted from pumping alone.

4. Three rheumatoid arthritis patients treated with typhoid vaccine-autohemotherapy alone showed prompt remission of their disease, but no alleviation of their peripheral fibrositic and vasomotor symptoms.

5. One patient with Marie-Strümpell arthritis was treated with a combination of Speransky spinal pumping and typhoid vaccine-autohemotherapy with negative results.

6. Four rheumatoid arthritis patients, who had initially been treated with Speransky pumping alone but whose activity continued, were later treated with a combination of spinal pumping and fever therapy. Three of these patients promptly went into remission while the fourth was only slightly benefited.

7. Two patients with probable rheumatoid arthritis were treated with a combination of pumping and fever; both improved markedly, were reambulated and discharged in remission.

8. In the other 10 rheumatoid arthritis patients treated with the combination of pumping and fever, improvement was obtained. In 2 cases there were subsequent acute flareups in other joints; these latter cases are still hospitalized.

9. Of the 14 rheumatoid arthritis patients treated with a combination of Speransky spinal pumping and typhoid vaccine-autohemotherapy only 1 patient remained unimproved.

10. In all cases the major effect from use of the Speransky pumping was in alleviating peripheral fibrositic and vasospastic symptoms.

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DISSECTING ANEURYSMS

A PRESENTATION OF TEN CASE REPORTS AND A CORRELATION OF CLINICAL AND PATHOLOGICAL FINDINGS

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SINCE Shennan's classical monograph in 1934,²² the literature on dissecting aneurysms has increased progressively. An excellent review of recent American writings together with a report of 19 cases from this hospital was published in 1940 by Holland and Bayley.¹³ One of these cases was previously studied by Schattenberg and Ziskind²⁰ and a thorough discussion of the pathology is included in their paper. More recently Bay² and Reich¹⁷ have added an extensive bibliography on the subject. Both of these authors directed attention to the protean manifestations of the disease. We report 10 additional cases and present a correlation of clinical and pathologic findings, based on the material of others as well as our own.

Definition and Pathology. By definition, a dissecting aneurysm is hemorrhage within the media of the aorta, with or without an opening in the intima. It differs from a true aneurysm in that there is no sac formed by the walls of the vessel involved. Most recent authors, in accord with the views of Moritz¹⁶ on the pathologic changes found in dissecting aneurysm, describe typical findings of idiopathic cystic medial necrosis. This may or may not be associated with atherosclerosis or syphilitic aortitis. No definite, single etiologic factor is responsible for all cases. A number of degenerative processes may involve the aorta or its main branches and any one of them may prepare the way for a dissecting aneurysm.

The most common pathologic change in the aorta is atherosclerosis. However, this has been minimized as a cause of dissecting aneurysm. Atherosclerosis, more frequent in the aged, involves chiefly the intimal layer of the aorta with lipid deposits, calcification and ulceration. The media, which contains the principal supporting structures of the aortic wall, is not often seriously damaged in atherosclerosis. This probably accounts for the lack of correlation between atherosclerosis and dissecting aneurysm. The former, as mentioned above, is very common while dissecting aneurysm is a relatively rare disease. Nevertheless some degree of atherosclerosis is present in the majority of cases of dissecting aneurysm. Necrosis of the media of the aorta is characterized by basophilic mucinous substance in the media, with necrosis and weakening of the elastic tissue. This process appears to be the basic factor in most cases of spontaneous rupture of the media, with or without an intimal tear. The frequent finding of a large dissecting aneurysm without intimal rupture may be due to injury of the vasa vasorum by this process. The occurrence of necrosis of the media with atherosclerosis cannot be minimized as a contributing cause of medial dissection.

Syphilis may attack all layers of the aorta, but characteristically produces destruction of the media and elastic tissues. Small mononuclear round cell infiltration

of the wall of a saccular aneurysm is considered diagnostic of syphilis. This process may cause medial dissection but as an etiologic factor it is unimportant. The incidence of syphilis in the cases of dissecting aneurysm in this hospital approximates the incidence of syphilis in the general hospital population.¹⁴

Although the recent South American literature has proposed that mechanical trauma is an important factor in the pathogenesis of dissecting aneurysm, we have found nothing in the English literature or in our own experience to support this belief. Rheumatic fever, various toxic states and congenital vascular defects apparently play little, if any, rôle.⁶

The formation of a dissecting aneurysm usually involves a transverse tear 1 to 4 cm. in diameter through the aortic intimal layer. The blood then dissects down the previously weakened medial layer for a varying distance, depending on the degree of medial involvement. It may rupture into the aorta at another point and, with endothelialization of the channel, will produce a double aortic lumen. Occasionally there may be slight dissection down the media with apparent recovery, to be followed later by a second severe dissection resulting in death. Death may be due to external rupture through the adventitia into a body cavity or into the supporting tissue, or it may be due to extension with obstruction of the arterial trunks arising from the aortic tree. This obstruction is produced by further extension of the aneurysm from the media of the aortic layer down the medial layer of the branch with occlusion of the lumen by internal compression.

Incidence. As stated above, the incidence of dissecting aneurysm is quite low. Glendy *et al.*¹⁰ list its occurrence as 1 in 430 autopsies. The incidence in this hospital for the past 10 years (604,788 inpatient admissions) is 1 in 454 autopsies.

Clinical Picture. The aorta is the channel of blood supply to all systems of the body and any disturbance will produce pathologic changes. The manifestations

of obstruction to the blood supply are both protean and dramatic. Several excellent articles have recently appeared which emphasize the varied symptomatology resulting from medial dissection of the aorta.^{2,10,17,21} An increasingly large number of these cases are being diagnosed antemortem. With the early diagnosis in mind, and stimulated by the unusual findings at autopsy in 5 recent cases in this hospital, we are presenting 10 new cases. More important, we would like to direct attention to the close relationship between the clinical symptoms and the pathologic anatomy in each case.

A study of the pathologic specimens permits the division of cases into separate anatomic groups. According to the portion of the aorta involved, we suggest a division of cases of dissecting aneurysm into 8 groups (Fig. 2). Since the aorta is the site of practically all dissecting aneurysms, it is logical to begin at its origin and proceed along its course.

GROUP 1. The first vascular system to be involved by dissection of the aorta is that of the heart itself. The coronary arteries, as they arise from the aortic sinuses, are frequently compromised by disease of the ascending aorta (Fig. 1, A). Medial dissection in this region is usually followed by both a proximal and a distal extension of the dissection and may result in obliteration of the coronary circulation. Dissecting aneurysms of the intrapericardial portion of the aorta have been known to produce myocardial infarction,^{3,23} aortic insufficiency,⁹ cor pulmonale² and cardiac tamponade with pericarditis.¹ Of the 29 cases studied in this hospital, including 19 cases of Holland and Bayley,¹³ 9 have been complicated by hemorrhage into the pericardial cavity. The clinical criteria are substernal pain, dyspnea and shock associated with the electrocardiographic evidence of myocardial disease.

GROUP 2. Dissection of the thoracic aorta distal to the pericardial reflection may produce symptoms suggestive of carcinoma of the lung, hypostatic pneumonia

or massive hemothorax with shock.¹³ It is interesting to note that when rupture of a dissecting aneurysm occurs intrapleurally the hemothorax is almost always confined to the left pleural cavity. The clinical criteria are cough, hemoptysis, chest pain and clinical or roentgenologic evidence of compression of the lung (Fig. 1, A).

when there was selective obstruction of 1 carotid artery. The clinical criteria are homolateral blindness with contralateral flaccid paralysis, hemianesthesia and aphasia. These neurologic manifestations have not been recognized generally and in fact are probably quite rare, since the inferior aspect of the arch is more frequently involved (Fig. 1, A).

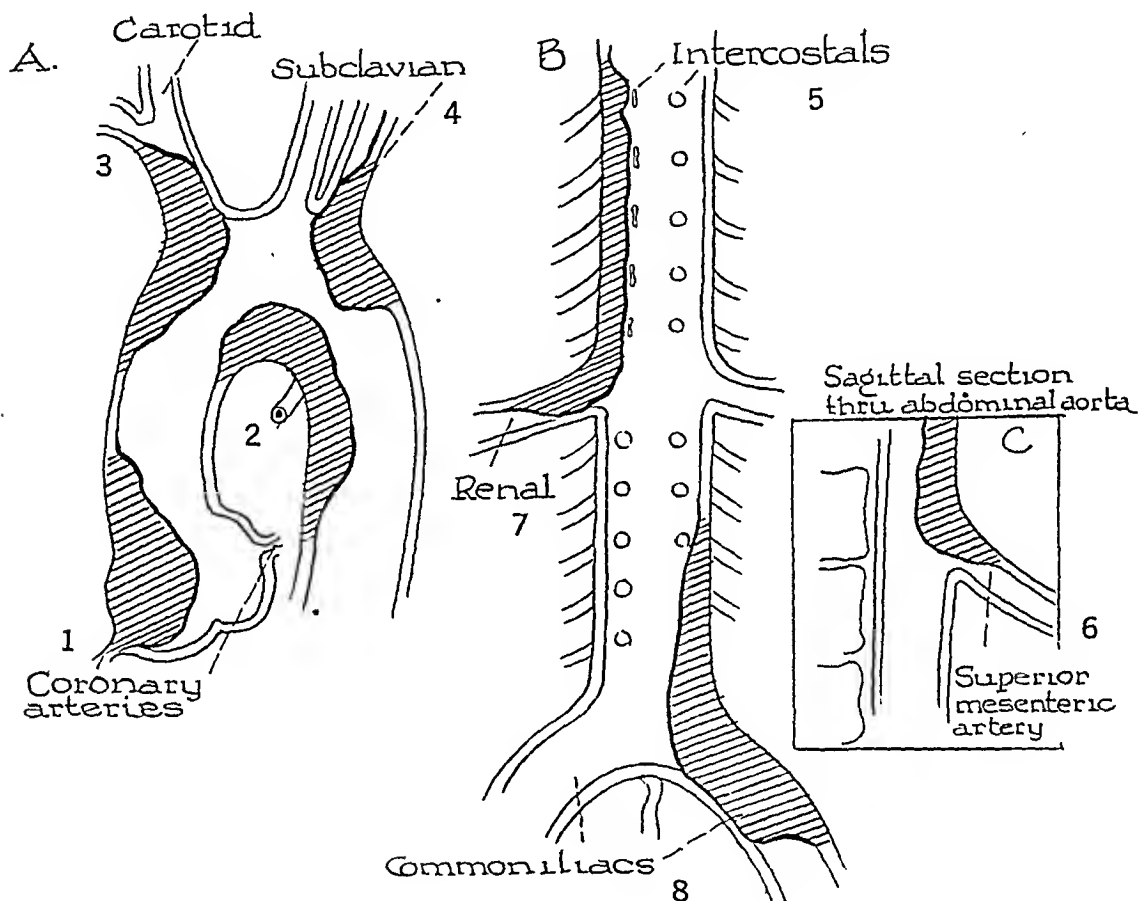


FIG. 1.—A, Sketch of a coronal section of the thoracic aorta showing occlusion by a dissecting aneurysm of (1) coronary artery, (2) bronchial artery, (3) carotid artery, (4) subclavian artery. B, Sketch of coronal section of the abdominal aorta showing occlusion of (5) intercostal arteries, (7) renal artery and (8) common iliac artery. C, Sagittal view of the abdominal aorta showing medial dissection of the anterior aortic wall resulting in occlusion of superior mesenteric artery (6).

GROUP 3. Involvement of the convex surface of the arch of the aorta may embarrass the carotid circulation and produce a clinical picture resembling cerebrovascular accident. Weisman and Adam²¹ in an excellent paper described a neurologic syndrome which occurs in such conditions. They used the term "carotid hemiplegia" to denote the changes found

GROUP 4. Obstruction of the subclavian artery or arteries by a dissecting aneurysm may produce symptoms similar to those of peripheral vascular disease. Ischemic necrosis of the upper extremity occurs as a result of sudden and complete obstruction of the subclavian artery^{1,21} (Fig. 1, A). These findings thought to be typical of thromboangiitis obliterans or arterial em-

bolism may result in surgical procedures for the relief of acute arterial obstruction.¹² The clinical criteria are sudden pain, cyanosis, loss of heat and flaccid paralysis of the arm, associated with an absence of pulsation of the brachial artery.

horn cells and the gray matter of the cord, especially in the thoracic area.¹¹ Occlusion of the ostia of the intercostal arteries in the lower thoracic and abdominal aorta may produce ischemic necrosis of the spinal cord (Fig. 1, B). The clinical picture of

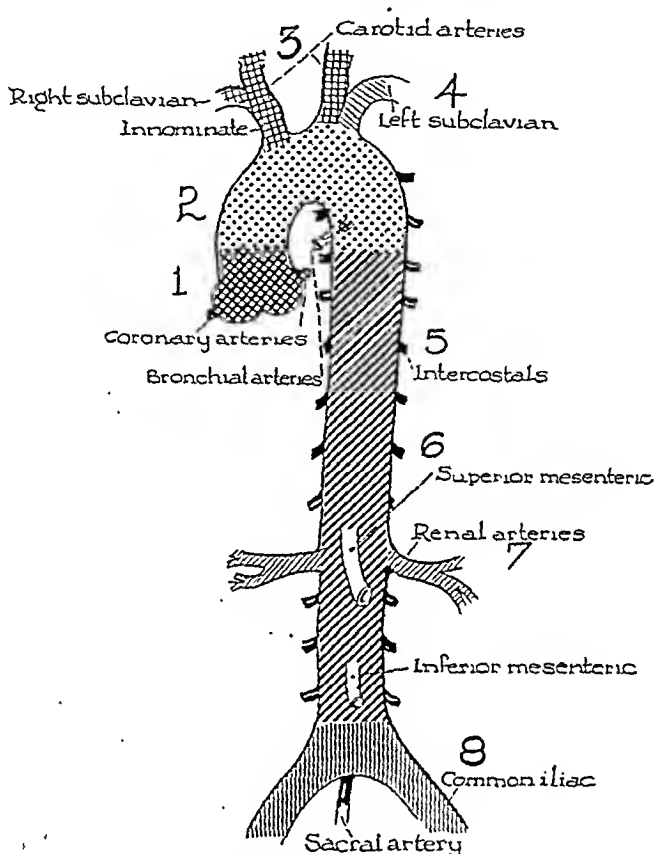


Fig. 2.—Schematic drawing demonstrating the 8 anatomic divisions of the aorta. The main arterial trunks arising from the aorta are indicated.

GROUP 5. The next main arterial system frequently implicated includes the intercostal, lumbar and sacral arteries. These paired segmental arteries arise from the posterior wall of the aorta at each of the lower 9 thoracic spaces, at 4 (or 5) lumbar interspaces, and several pairs also arise from the middle sacral artery. Each of these segmental arteries supplies a branch which enters the spinal canal via the intervertebral foramen and communicates with the anterior spinal artery. The anterior spinal artery furnishes the major portion of the blood supply of the anterior

transverse myelitis may result.²¹ Not all dissecting aneurysms produce this neurologic picture. Several factors determine whether the blood supply to the anterior spinal artery will be impaired. The intercostal, lumbar and sacral arteries vary as to their site of origin from the posterior wall of the aorta.⁷ Dissection of the aorta usually occurs on the anterior or ventral wall and frequently extends in a spiral fashion. Weisman noted that most of his cases of neurologic complications were in elderly individuals in whom the circulation had already been impaired by atherosclerosis.

sis. The clinical criteria are flaccid paralysis and diminished sensation distal to the obstruction of the intercostal arteries.

GROUP 6. Extraperitoneal rupture or dissection into the mesenteric arteries may simulate intrinsic disease of the gastro-intestinal tract (Fig. 1, C). Symptoms suggestive of mesenteric thrombosis, ileus, malignancy of the bowel or hernia may confuse the examiner and lead to surgical intervention. The diagnosis of acute colitis or enteritis may be suggested by the sudden onset of dysentery associated with cramping abdominal pain. Holland and Bayley reported a case of gangrene of the entire small intestine resulting from involvement of the superior mesenteric artery by a dissecting aneurysm.¹³ The clinical criteria are sudden onset of abdominal pain, hematemesis or melena, together with physical or roentgenologic evidence of intestinal obstruction.

GROUP 7. The renal arteries are frequently compressed by dissection of the abdominal aorta and the resulting infarction of the kidney may produce symptoms compatible with renal colic⁸ or nephrolithiasis.⁴ The clinical criteria are sudden onset of lumbar pain, with or without radiation into the groin, associated with the laboratory findings of albumin, casts and blood in the urine. Medial dissection of the lower abdominal aorta usually involves several of the large arterial trunks and the above criteria may facilitate clinically the exact localization of the aneurysm³ (Fig. 1, B).

GROUP 8. Last, but by no means infrequent, is the involvement of the common iliac arteries by extension of an abdominal aneurysm. Medial dissection frequently begins in the arch and extends along the entire length of the aorta, terminating usually at the first branch of the common iliac artery (Fig. 1, B). The resulting arterial obstruction may produce ischemic necrosis of the extremity. The criteria are sudden pain, cyanosis, loss of heat and flaccid paralysis associated with an absence of pulsation of the femoral artery.

Discussion. An appreciation of the basic pathology common to all cases of dissecting aneurysm will improve the accuracy of the clinical diagnosis. As stated in the premise, we believe that the anatomic division of such cases will aid the clinician in correlating the symptoms with the actual pathologic changes. Classically the symptoms of dissecting aneurysm consist of sudden, severe, "knife-like" pain in the substernal area followed by extension of the pain posteriorly and inferiorly. A considerable number of these cases, however, begin with pain below the diaphragm associated with symptoms suggesting primary gastro-intestinal or genitourinary disorders. As a result, disease of the abdominal aorta is usually not suspected.

We do not wish to imply that all cases of dissecting aneurysm fall into a single anatomic group. On the contrary, the majority of cases coming to autopsy show involvement of several vascular systems. The resulting symptoms may be used to advantage by the clinician as a guide in determining the origin, extension and terminal complications of dissecting aneurysms.

In the past 6 months we have autopsied 5 cases of dissecting aneurysm. The correct diagnosis was made antemortem in 3 cases, 1 of which was diagnosed at surgical exploration of the abdomen. The remaining 5 cases were taken from the files of this hospital.

Case Report. CASE 1. A 50 year old colored male was admitted with a history of sudden, severe, cramping abdominal pain of 1 week's duration. The pain extended straight back to a point just beneath the scapula and around to the right flank. He vomited a considerable amount of bitter material and felt some relief. Since the first attack, he had had several recurrences of pain but no further emesis. The patient was well developed and well nourished and appeared about the stated age. There was a marked arcus senilis and the pupils reacted to light and accommodation. The lower lids were very pale. There was no general glandular enlargement but the epitrochlear

and inguinal nodes on the right were palpably enlarged and not tender. The heart was enlarged to the left, with the point of maximal impulse located in the sixth interspace 11.5 cm. to the left of the midline. There was a localized thrust at the apex. The rhythm was regular and the aortic second sound was accentuated. The blood pressure was recorded as 230/150. The peripheral arteries were sclerotic. The lungs were clear to percussion and auscultation. In the abdomen, there was a slight prominence at the level of the umbilicus. Peristalsis was visible on the left. The left rectus muscle was slightly more resistant than the right. Pressure over this area caused severe pain. In general the abdomen was flaccid and no viscera were palpably enlarged. An area of pain was located in the epigastrium 3 fingerbreadths below the xiphoid process.

The patient was allowed bathroom privileges and he remained asymptomatic for 2 days except for occasional bouts of nausea. He experienced pain in the right shoulder for which he was given sedation. An Ewald test meal was conducted the 2nd hospital day and his condition was considered good. After returning from the bathroom, he suddenly became unconscious and died within 10 minutes.

The clinical diagnoses entertained were gall bladder disease, malignancy of the stomach and tabetic crisis.

Postmortem examination revealed a massive hemothorax on the left with collapse of the lung. A dissecting aneurysm measuring 2 cm. in thickness and 8 cm. in width was located on the convex surface of the descending aorta. The aneurysm had ruptured on its convex surface into the left pleural cavity. On opening this aneurysm, it was seen to communicate with the aorta through a ragged irregular defect 1 cm. in diameter. The aortic wall separating the aneurysm from the lumen of the vessel was very thin and friable. Medial dissection had extended down into the abdomen as far as the bifurcation of the aorta and along the right common iliac artery to its first branch. The aneurysm did not completely surround the aorta but left about one-third of its circumference intact along the posterior surface. The intimal lining of the aorta in the abdominal region presented no gross changes.

Comment. This case represents an involvement of the blood supply to the gastro-intestinal system resulting in ischemic necrosis and is an example of Group 5. The rupture into the left pleural cavity was undoubtedly terminal and accounted for the sudden exitus.

CASE 2. This 32 year old colored male was admitted to the ward in a comatose condition. The clinical course was progressively downhill and he died 7½ hours after admission. The clinical diagnosis was myocarditis and hypostatic pneumonia.

Postmortem examination revealed a dissecting aneurysm of the descending portion of the thoracic aorta and upper portion of the abdominal aorta. There was a rupture into the left pleural cavity as well as a massive hemoperitoneum from rupture into the abdominal cavity.

Comment. The rapid course in this case suggests sudden massive hemorrhages both above and below the diaphragm as the cause of death. The symptoms and pathologic findings place this patient in Group 2.

CASE 3. A 48 year old white male was admitted with a sudden onset of precordial pain and indigestion which the patient attributed to eating oysters and drinking whisky. Shortly after admission his temperature, pulse and respiration were recorded normal. He refused to go to bed and said he wanted to go home in the morning. The morning after admission while sitting up in bed, he had a second attack of precordial pain, became unconscious, sweated profusely and died 30 minutes later. The clinical diagnosis was coronary thrombosis.

Postmortem examination revealed an enormous (4000 cc.) blood clot in the left pleural cavity. In the first portion of the descending aorta there was a wide annular dissecting aneurysm which communicated with the aorta. On tracing the extent of the aneurysm down the thoracic aorta, hemorrhage was found within the mediastinum and finally a rupture into the pleural space on the left. The aorta showed numerous raised, edematous, intimal plaques with wrinkling and scarring throughout its course. Section showed a typical luetic process with medial degeneration and round cell infiltration about the small vessels in the adventitia and media.

Comment. Hemorrhage into the mediastinum produced symptoms suggestive of cardiac disease but no lesions were demonstrable in the heart itself. The massive hemothorax on the left was acute and was the immediate cause of death. This case falls into Group 2.

CASE 4. A 54 year old white male was admitted with a history of dizzy spells for 2 years. He had had dyspnea on exertion for the past 3 weeks. The dyspnea had become worse but was not associated with pain. Shortly after the appearance of the dyspnea, edema of the legs and abdominal swelling occurred. Edema was progressive and the patient had been bedridden for the past 2 weeks. Examination on the ward revealed a well-developed and well-nourished man who was dyspneic on exertion. There was impaired resonance in the right axillary region together with a decrease in intensity of breath sounds. Moist râles were heard at both bases. The heart was moderately enlarged to the left with a rate of 98. Frequent ectopic beats were heard. There was a soft systolic murmur at the apex and the apical second sound was sharp and snapping. The aortic second sound was "bell-like." The blood pressure was 204/154 in both arms. The liver was markedly enlarged, extending 5 cm. below the costal edge. There was dullness in both flanks and slight bilateral edema of the legs.

The patient was digitalized, placed on a low salt diet and instructed to remain in bed. He refused to stay in bed but nevertheless showed some symptomatic improvement until the 7th hospital day. While sitting by the bed, he was seized by a severe pain in the chest and collapsed across the bed. Shock rapidly intervened and in spite of nasal oxygen, morphine and aminophyllin, the patient expired 2 hours after the onset of pain. The clinical diagnoses were hypertensive cardiovascular disease and cerebrovascular accident.

Postmortem examination revealed the pericardial cavity distended with 300 cc. of fresh blood. A hematoma was found at the base of the heart, involving the adventitia of the aorta and the pulmonary artery. The base of the aorta showed an atheromatous ulcer which had penetrated almost to the adventitia. There was a large hematoma in the right lower quadrant of the abdominal

cavity. Section through the base of the left ventricle showed subepicardial hemorrhage and extensive atherosclerosis of the coronary arteries. Section of the aorta just above the valves showed necrosis of the media and extensive hemorrhage into the adventitia.

Comment. It is difficult to say how great a part the dissecting aneurysm played in the early course of this man's disease. His death by cardiac tamponade places this case in Group 1.

CASE 5. This 59 year old white male was seen in the admitting room and expired 15 minutes later. He gave a history of sharp pain in the lower right quadrant of the abdomen and right hip which had appeared suddenly 2 hours previously. He had been healthy all his life, with no complaints other than a chronic inguinal hernia for which he wore a truss. The morning of admission, the patient suddenly fell to the floor and was forced to lie there unable to use his right leg because of "numbness." Pain was severe and was eased only by intermittent flexion of the hips. The right inguinal hernia was easily reduced by the ambulance physician and the patient was brought to the hospital. His chest was hyperresonant to percussion but otherwise normal. The heart sounds were inaudible but the pulse was not rapid. Blood pressure was recorded only once as 96/84. A small non-tender mass was palpable per rectum just above a slightly enlarged prostate. A bloody diarrhea appeared during the examination in the admitting room. The patient appeared to be *in extremis* and the examination was curtailed in order to get the patient to the ward as quickly as possible. Death occurred 15 minutes after admission. The clinical diagnoses were strangulated hernia, multiple emboli and acute colitis or enteritis.

Postmortem examination revealed the pericardial sac filled with 250 cc. of fresh blood. In the lumen of the small intestine was a pale, red, viscid fluid. The mucosa was congested but no definite bleeding site was established. The large bowel contained a small amount of similar fluid. No tumor mass or ulceration was found. No thrombus or other occlusion of the mesenteric vessels was demonstrated. The media of the thoracic aorta was completely separated by a large blood clot. In the abdominal aorta only portions of the wall were separated.

The medial dissection extended down to the bifurcation of the abdominal aorta. The site of rupture into the pericardial cavity could not be found. In the intima were numerous superficial, yellow, atheromatous plaques with some ulceration but no definite communication with the media was seen. Section of the aorta revealed a disappearance of the elastic fibers of the media with thickening of the subintimal layer.

Comment. As stated in the discussion of Group 6, we feel that in spite of the negative findings at autopsy, the rectal bleeding of the viscid red fluid found in the gastro-intestinal tract were related to interference with the mesenteric blood supply. Similar cases have been reported.¹³ Likewise the involvement of the pericardial cavity and the right common iliac artery places this unusual case in 3 of the anatomical groups. Disturbance of blood supply was evident in the heart, gastro-intestinal tract and in the lower extremity (Groups 1, 6 and 8).

CASE 6. For the previous 3 months this 67 year old white male had noted pain in the chest, cough and frequent hemoptyses. Lying on the right side relieved the pain. There was marked burning on urination. He denied all previous illnesses except "influenza." Examination on admission revealed a temperature of 99° F., pulse 100, respiration 30 and blood pressure 134/86. The percussion note over the right chest was hyper-resonant. There were exaggerated breath sounds over the same area. The percussion note over the left base was dull, breath sounds were absent and moist râles were heard on auscultation. An erect posterior-anterior Roentgen ray of the chest revealed a marked enlargement of the left hilar shadow, with opacity radiating peripherally. The lower half of the left hemithorax was opaque. The course in the hospital was progressively downhill. The patient complained of low back pain for which he was given narcotics. A non-productive cough continued and bronchoscopy was scheduled. After several days in the hospital, he was given scopolamine, 0.03 mg., and sent to the bronchoscopy room. Endoscopy was deferred, however, because the patient appeared too weak. He returned to the ward in poor condition and failed rapidly. He died quietly on the 30th hospital

day. The clinical diagnosis was bronchogenic carcinoma of the left lung.

Postmortem examination revealed both lungs adherent to the parietal pleura. After these adhesions were cut, a large fairly firm mass was found between the left costovertebral angle and the left lung. There was no direct attachment between the lung and this tumor mass, but it was continuous with the descending aorta. The upper portion of the pericardial cavity was distorted by the presence of a firm round tumor mass measuring 5 by 6 by 8 cm. It was attached to the ascending aorta. Four cm. above the aortic ring was an opening in the intima of the aorta. The dissecting aneurysm formed at this point measured 5 by 6 by 8 cm. Its wall was 3 mm. in thickness after the well-organized blood clot was removed. The arch of the aorta contained both atheromatous and luetic plaques. Three cm. below the arch was another opening in the intima 1 cm. in diameter. From this orifice arose a second large dissecting aneurysm measuring 19 by 17 by 11 cm. which extended from this point down to the diaphragm. Its wall was composed of layered blood clots, some of which were well organized. The aneurysm reentered the lumen of the aorta 2 cm. above the diaphragm. In the right iliac artery as it crossed the brim of the pelvis, was a third small dissecting aneurysm 2 cm. in diameter.

Comment. This case adds another member to the long list of diseases which may simulate bronchogenic carcinoma. The symptoms presented here were undoubtedly due to the "chronic" dissecting aneurysm of the descending aorta which produced disturbance to the pulmonary artery on the left. This is an example of Group 2.

CASE 7. Two days prior to admission this 72 year old white male experienced sharp pain localized in a left inguinal hernia which had been present for 8 years. At the onset of pain, the hernia became for the first time irreducible and associated with nausea and vomiting. On admission the pulse was 90 and blood pressure was 114/70. He did not appear severely ill at the time. The abdomen was distended, peristalsis was increased and a tinkling sound was heard over the entire abdomen. Tenderness and rigidity were noted over the lower left quadrant. A small mass was palpable around the internal inguinal ring and the indirect

inguinal hernia was not reducible. Rectal examination was not contributory. At operation soon after admission, a small indirect hernia was discovered. The cord structures contained large blood clots which had apparently dissected down from above. The hernia was reduced and the abdomen explored through a larger incision. A massive retroperitoneal hemorrhage was found with blood clots extending from the left perirenal area to the spermatic cord. No active bleeding was noted and the peritoneal cavity appeared normal. His condition was good on closure and the blood pressure was recorded as 104/90. Approximately 6 hours after admission, the patient suddenly became violently restless, pulled out his suction and intravenous tubing, went into deep shock and died. The clinical diagnoses were incarcerated left inguinal hernia and retroperitoneal hemorrhage, probably dissecting aneurysm.

Postmortem examination revealed numerous, elevated, yellowish plaques throughout the intima of the aorta. Many were calcified with superimposed ulceration. The latter had pale, gray, friable mural thrombi attached to their surface. Nine cm. above the bifurcation of the aorta there was a 2 cm. transverse intimal tear which communicated with a large dissecting aneurysm. The aneurysmal sac had completely encircled the aorta and extended from the intimal tear distally to the bifurcation. The aneurysm was filled with friable, yellow, atheromatous material and clotted blood. The retroperitoneal space contained clotted blood which extended from the diaphragm above, to the sacral region below and laterally to the edge of the rectus muscle.

Comment. As was proved at surgery, this is an example of dissecting aneurysm producing intestinal ischemia and obstruction. The retroperitoneal hemorrhage had dissected into the narrow inguinal canal and had interfered with the circulation to the incarcerated bowel. This is an example of Group 6.

CASE 8. This 67 year old white male entered the hospital for the relief of urinary difficulties of 10 months duration. He complained of frequency, dysuria and radiating pain from the groin to the penis whenever he urinated. There had been no acute onset of symptoms and he was admitted for elective treatment of prostatic calculi and acute

cystitis. On admission his pulse was 78, blood pressure 130/85, and a thorough physical examination revealed no other systemic disorders. A cystoscopic examination revealed a bladder tumor which was biopsied and the pathologist reported squamous cell carcinoma. Chills and fever followed the cystoscopic examination and he was not considered a good operative risk. Two weeks following admission when his condition had improved, a suprapubic urethral transplant and cystectomy were attempted under local anesthesia. After 50 cc. of 2% procaine had been injected beneath the rectus fascia, the patient suddenly complained of pain in the right hip, began to breathe deeply and expired. The clinical diagnosis was squamous cell carcinoma of the bladder.

Postmortem examination revealed generalized raised, yellow, calcified intimal plaques throughout the aorta. In the posterior wall of the abdominal aorta, 4 cm. below the diaphragm, a 4 cm. transverse intimal tear was found. This ragged opening was located at the lower edge of a large ulcerated atheromatous plaque and communicated with a dissecting aneurysm which completely encircled the aorta and extended distally to involve 5 cm. of both common iliac arteries. The aneurysmal cavity contained friable, thick, chalky material and clotted blood. The intimal surface of the aorta overlying the aneurysmal sac, was covered with a large mural thrombosis. Mural thrombi were also found in the iliac arteries, especially the right, which was almost completely occluded.

Comment. The sudden pain in the right hip was most likely due to the terminal and sudden occlusion of the right common iliac artery. Death was caused by shock due to massive hemorrhage into the aneurysmal sac surrounding the abdominal aorta. This is an example of Group 8.

CASE 9. While playing cards, this 58 year old white male suddenly developed pain in his throat resembling a mass of food caught there. The pain was unbearable at first but after he walked a few minutes it became less intense and seemed to settle in the midsternal region. After 2 hours of rest, he walked home, took a mild laxative and went to bed. The pain persisted for the next 6 days as a mild ache, aggravated by cough. On the day of admission, while rising from bed, he coughed and immediately experienced severe pain which seemed to shoot up

his back from his coccyx and settle in his abdomen. The pain was continuous and more severe when the patient was in the upright position. A cramping sensation was noted 6 inches above and below the knees. He was admitted 7 days after the onset of pain. There was a history of a penile lesion at 21 but he denied treatment for lues. He was well developed and well nourished and appeared severely ill. He complained bitterly of pain in the lumbar area which was aggravated by change in position. The heart was enlarged to percussion; the sounds were weak and distant. There was a diastolic murmur over the apex, loudest in the aortic area and a systolic murmur at the base of the heart. The pulse was 64 and the blood pressure 108/98. All peripheral pulses were equal bilaterally. The abdomen was tender in the umbilical area but no masses or distention were noted. There was slight edema of the feet. Superficial and deep reflexes were normal. A spinal tap revealed a pressure of 130 mm. of water; the fluid was clear and chemical analysis showed protein of 30 mg. per 100 cc., chloride of 826 mg., glucose of 59 mg., a positive Kline and Kolmer test for syphilis and a colloidal gold curve of 0011111100. Urinalysis revealed granular and hyaline casts with white blood cells in clumps. An electrocardiogram was reported as being within normal limits. Twelve days after the onset of his pain and on his 5th hospital day, he suddenly complained of pain in his chest and very quickly died. The clinical diagnosis was dissecting aneurysm of the aorta.

Postmortem examination revealed the pericardial sac to be greatly distended, blue-black in color and filled with 500 cc. of clotted blood, many of the clots being antemortem. No tears were noted in situ but on removing the organs intact, a transverse intimal tear 1 cm. in length was found at the base of the innominate artery. This tear was into the medial layer of the aorta and the resulting aneurysm extended proximally into the pericardial sac and distally to the bifurcation of the abdominal aorta. Extension into the pericardial sac was through several pin-point openings of the adventitia at the base of the aorta. The dissection almost encircled the aorta but in the abdominal portion was principally posterior and lateral. Complete obstruction of the lumen of the thoracic intercostal arteries was found as well as involvement of the

first 1 cm. of both renal arteries. The renal arteries contained no thrombi however, and their lumina were not significantly narrowed. The intima of the aorta contained a few raised yellow plaques and the valves had some calcification. The coronary arteries were patent throughout.

Comment. This case was diagnosed clinically on the basis of a sudden onset of severe chest pain followed by extension posteriorly and into the lower spine. The negative findings on electrocardiographic examination suggest that the hemopericardium was a terminal affair and probably accounted for the sudden death. Similarly, the sudden death prevented the diagnosis of transverse myelitis which this man would probably have exhibited had he lived. This is an example of Groups 1 and 4.

CASE 10. While drinking whisky, this 59 year old colored male developed pain in the right chest, inferiorly and posteriorly. The pain progressed to the posterior portion of the left chest and from there circled on either side of his trunk to meet anteriorly. Immediately he experienced numbness of the lower abdomen and legs. He was admitted 2 hours later with flaccid paralysis of both lower extremities. On admission his pulse was 70, blood pressure 100/60 and temperature 96.4° F. The patient was obviously in shock, being cold, clammy, perspiring and complaining of hot flashes. The heart was enlarged to percussion and the rhythm was regular. There was a loss of sensation below the level of the umbilicus. After an initial chill, he slept all night and had no further complaints until 19 hours after the onset of his illness. At this time he suddenly became dyspneic, cold and clammy and his pulse was rapid and "thready" in character. The blood pressure was not determinable. Treatment for shock was instituted but he became drowsy and an obvious anemia developed due to massive internal hemorrhage. The blood pressure was recorded terminally as 80/60 but the patient failed rapidly and died on the 2nd hospital day. The clinical diagnosis was dissecting aneurysm of the aorta with involvement of the vertebral artery.

Postmortem examination revealed an aorta which showed evidence of both syphilis and atherosclerosis. The ascending portion of the arch showed longitudinal wrinkling and an occasional pearly gray, waxy plaque, as well

as a few yellow raised plaques without ulceration. A careful search of the intima revealed no tear. However, beginning at the junction of the arch and the descending aorta, the medial layer was separated by a large friable blood clot. This dissecting aneurysm measured 5 mm. in thickness and extended down to the bifurcation of the aorta and into the left common iliac artery for a distance of 3 cm. The dissection had occurred posteriorly and laterally and at no place encircled the aorta. The left renal artery was involved by an extension of the medial dissection and the lumen was further occluded by an antemortem thrombus. The aneurysm had ruptured medially into the mediastinum and it contained many large blood clots. A small hematoma was noted beneath the pericardium about the base of the pulmonary artery. Both pleural cavities contained clotted blood from an extension of the mediastinal hemorrhage. Distally the aneurysm had penetrated the aortic hiatus and a large retroperitoneal hemorrhage was present.

Comment. Clinically this man presented the symptoms of transverse myelitis with a sensory level at the tenth dorsal segment and a flaccid paralysis below this level. The pathologic findings were consistent with an infarction of the anterior spinal artery in the lower thoracic and lumbar areas. This was the third case to be diag-

nosed antemortem and is an example of Group 5.

Summary. 1. Ten cases of dissecting aneurysm are presented with a detailed study of the clinical and the pathologic findings.

2. A brief review of the pathology is included, together with a discussion of the relative etiologic importance of (a) atherosclerosis, (b) idiopathic cystic medial necrosis and (c) syphilis.

3. The incidence of dissecting aneurysms in this hospital for the past 10 years is 1 in each 454 autopsies.

4. The division of all cases of dissecting aneurysm into 8 anatomic groups is suggested and a correlation is made between the symptomatology and the pathologic findings. We believe this will aid in the antemortem diagnosis.

5. The manifestations of the 8 anatomical groups arise from a disturbance of the circulation to (1) the heart, (2) the lungs, (3) the brain, (4) the upper extremity, (5) the spinal cord, (6) the gastro-intestinal tract, (7) the genito-urinary tract and (8) the lower extremity.

6. The schematic drawings are included illustrating the 8 anatomic groups.

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PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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THE THROMBO-EMBOLISM PROBLEM

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ALTHOUGH much has been learned during recent years about intravenous clotting and pulmonary embolism, the fundamental mechanisms involved and the pathologic physiology are not as yet well understood. A large part of our present knowledge has resulted from careful postmortem examinations and statistical studies of patients with thrombo-embolic disease. Since the work of Rössle,⁵⁵ Neumann⁴⁸ and Frykholm²⁵ it has become widely recognized that the majority of venous thrombi originate in the lower extremities, particularly in the deep veins of the calves and feet. Ninety-five per cent of the thrombi which lead to fatal pulmonary embolism are believed to occur in the veins of the legs.¹ The importance of regarding *phlebothrombosis* and *thrombophlebitis* as fundamentally different processes, as emphasized by Ochsner and De Bakey,⁵¹ has been widely accepted. In 209 autopsies in which there was thrombosis of the leg veins, Hunter and his associates³² found no evidence of phlebitis in 92%. Others

believe, however, that phlebothrombosis becomes thrombophlebitis in the later stages and that in many patients there are characteristic features of both processes.^{8,22,31} Ochsner⁴⁹ has repeatedly emphasized that in thrombophlebitis, in which there is firm attachment of the clot to the vein wall, there is little danger of embolism, while phlebothrombosis is the common precursor of pulmonary embolism.

The incidence of recognizable thrombophlebitis in postoperative surgical patients is between 1 and 2%.³¹ The incidence of phlebothrombosis is not known because of the frequent absence of signs and symptoms. The finding of thrombosis of the lower extremities in more than 50% of persons dying of any cause in the latter half of life³² suggests that phlebothrombosis may occur more commonly than hitherto suspected. Fatal pulmonary embolism occurs about once in every thousand operations³³ and is the cause of about 5% of postoperative deaths.⁴⁴

Although the basic abnormalities which

precipitate intravascular clotting are not known, a number of predisposing factors have been discovered. These have been reviewed by us in a recent report.³⁵ Intravenous clotting is thought to be precipitated by slowing of the circulation, increased coagulability of the blood and injury to veins or perivenous tissues. In most patients with thrombo-embolic disease one or more of these factors may be shown or presumed to be present. Ochsner⁴⁰ believes that the fundamental abnormality is an increased coagulability of the blood, with circulatory stasis the precipitating factor. It appears likely that the observations of Knisely and his associates³⁷ on sludging of the blood may be helpful in clarifying the etiology of thrombosis. Recently two ingenious tests have been devised to demonstrate increased coagulability of the blood. These are the heparin tolerance test of De Takats²⁰ and the modified prothrombin test of Brambel.¹¹ Both have shown an increased tendency of the blood to clot in patients with previous or active thrombo-embolic disease, following serious injuries, major operations, and in Buerger's disease. Unfortunately neither test is sufficiently sensitive to detect subclinical thrombosis or to predict the occurrence of thrombosis.

A number of clinical factors have been shown to increase the incidence of thrombosis and embolism, the most important being heart disease, major operations, severe injuries, obesity, cold weather and other vasospastic influences and debility. Fatal pulmonary embolism occurs more commonly in males than in females, the ratio being about 3 to 2. Fatal pulmonary embolism is predominantly a disease of the latter half of life. At the Hospital of the University of Pennsylvania 92% of all fatal embolisms occurred in patients above the age of 40.³⁵ In some instances fatal embolism may occur in young individuals in apparent good health.²⁸

PROPHYLAXIS. A prophylactic approach to the problem of thrombo-embolism is desirable for two reasons.³⁶ First, thrombosis frequently causes permanent damage

to the femoral veins and their valves and is followed by the syndrome of chronic venous insufficiency, with edema, fibrosis and ulceration. This condition causes much suffering and disability, and treatment is often disappointing. Second, fatal pulmonary embolism often occurs without warning signs or symptoms that thrombosis has occurred. Death in such instances can be prevented only by the prevention of thrombosis or by the use of measures designed to prevent embolism if thrombosis occurs.

Ochsner⁵⁰ believes "that most, if not all, cases of intravenous clotting can be prevented by the institution of prophylactic measures." Many general prophylactic measures have been proposed, and a number are in current use. The purpose of most of them is to prevent circulatory stasis. In most surgical clinics there is emphasis on deep breathing and leg exercises, prompt correction of anemia and electrolyte imbalance, frequent change of position in bed and prevention of hypotension and abdominal distention. Ravdin stresses avoidance of heavy sedation. Prophylactic measures which deserve special comment are early ambulation, anticoagulants and femoral vein ligation.

EARLY AMBULATION. Since thrombosis and embolism follow confinement to bed in most instances, an approach toward normal, ambulatory activity during illness or following operation would appear to be a logical prophylactic measure. This was first attempted in 1899,⁵⁴ but was not practiced extensively by surgeons in this country before 1940, chiefly because of the fear of wound disruption. The evidence regarding the effectiveness of early ambulation in preventing thrombosis and embolism is conflicting. Zava⁵⁵ in more than 6000 patients had not a single embolism. Leithauscr,⁴⁰ whose recent book reviews the literature on this subject, noted only 2 instances of thrombosis and no embolism in more than 2000 patients who were ambulatory on the day of operation or the first postoperative day. Jorpes,⁵³ on the other hand, presents evidence that "medi-

cal gymnastics and early ambulation" will reduce the incidence of thrombosis only to 0.61 % in surgical patients and that the mortality in these patients is 20 %. Powers,⁵³ in a careful analysis of 1519 patients following major operations, concluded that early ambulation and active exercises increased the incidence of thrombo-embolic complications slightly but reduced the incidence of fatal embolism by about 50 %. This has also been the experience of others.¹⁰ It has been repeatedly stressed that early ambulation means actually walking, rather than sitting in a chair, which may diminish venous return. Leit-hauser⁴¹ believes that walking on the day of operation may be an important factor in his success with this method.

PROPHYLACTIC ANTICOAGULANTS. Heparin was first used prophylactically by Crafoord¹⁷ as early as 1935, and in 1941 he¹⁸ reported the results in 325 patients, in whom thrombo-embolic complications were virtually eliminated. The experience of Murray⁴⁶ in postoperative patients and Leissner³⁹ in postpartum patients was similar. Jorpes³⁴ believes that because of the risk of hemorrhage and the expense it is not possible to give heparin prophylactically to all or the majority of postoperative patients but that it should be used prophylactically in patients in whom there is an unusual risk of a thrombo-embolic complication.

Dicumarol has also been used prophylactically, relatively large series being reported by Bruzelius,¹³ Allen³ and Barker and his associates.⁶ All have noted an apparently significant reduction of thrombo-embolic complications. In the most recent review of the use of dicumarol at the Mayo Clinic,⁵ minor hemorrhage (epistaxis, hematuria and localized ecchymosis) was noted in 3.4 % of 1983 postoperative patients and serious bleeding (from operative wounds or from the gastrointestinal tract) in 1.8 %. Two patients died from hemorrhage although the authors are not certain that the fatal hemorrhage could be definitely attributed to the effect of dicumarol.

In comparison with dicumarol the advantages of heparin are its prompt effect on the coagulability of the blood and the prompt neutralization of its effect by protamine, while disadvantages are its high cost and the necessity for frequent or continuous parenteral administration. Walker and Rhoads⁵⁷ have shown that heparin and dicumarol have a complementary effect and that this may be used to advantage by giving them simultaneously. In dicumarinized patients with a prothrombin time of 20 to 30 % of normal, intramuscular injections of heparin at intervals of 6 to 12 hours result in a prolonged and more evenly maintained elevation of the coagulation time. Loewe and his associates⁴³ have advocated the subcutaneous administration of heparin in Pitkin's menstruum, which delays absorption and reduces the amount of heparin required.

Dicumarol is inexpensive and may be given by mouth. Disadvantages of dicumarol are the unpredictable response in many individuals, the lack of a reliable method of restoring the prothrombin to normal promptly if hemorrhage occurs, the exacting laboratory procedure required for control, the delay in reduction of the prothrombin to effective levels for 48 to 72 hours, and the contraindications to the use of this drug in many of the patients most in need of protection.

Anticoagulants should not be used unless adequate personnel and equipment are available for careful laboratory control.

PROPHYLACTIC VEIN LIGATION. Recognizing that the above prophylactic methods are not always applicable or effective in preventing thrombosis and embolism, prophylactic femoral vein ligation has been proposed as a means of preventing fatal embolism in patients in whom the mortality from this cause is comparatively high. In elderly patients with hip fractures, for example, pulmonary embolism has been found to be a common cause of death.⁵² Allen³ found that in 110 consecutive patients with hip fractures death from massive embolism occurred in 11 (10 %). In another consecutive series of 110

patients in whom bilateral femoral vein ligation was done prophylactically, there were no deaths from embolism. The largest series of prophylactic femoral ligations reported has been done by Allen.³ In 458 patients with prophylactic ligation death from embolism occurred in only one, in whom a thrombus was found in the proximal segment of the superficial femoral vein ligated 3 cm. distal to the profunda femoris. In a comparable control series of 458 patients without prophylactic ligation, death from embolism occurred in 26. These figures suggest that 458 prophylactic ligations saved the lives of 25 patients. In the 458 patients with prophylactic ligation "phlebitis" occurred in only 5 while in the control series it occurred in 55. Allen states that "it comes as an added dividend that thrombophlebitis is likewise prevented."

In 2 recent elderly patients with hip fractures at the Hospital of the University of Pennsylvania, death from massive embolism occurred following prophylactic superficial femoral ligation. In both the ligature had been placed about 5 cm. distal to the common femoral vein, and there was evidence at autopsy that a thrombus had formed in the isolated proximal segment of the superficial femoral vein. It thus appears evident that maximal protection is afforded only if the superficial femoral is ligated at its junction with the profunda femoris. Recent anatomic studies demonstrate that identification of the junction of the superficial and deep femoral veins may necessitate considerable dissection.²³

Recent experiences of Erb and Schumann²⁴ with prophylactic ligations in elderly patients have not been favorable. In a series of 100 consecutive patients with hip fractures at the Philadelphia General Hospital, bilateral superficial femoral ligation (at the junction with the profunda) was done in alternate patients. Death from massive pulmonary embolism occurred in 2 of the 50 ligated patients and in 2 of the 50 not ligated. In addition, non-fatal pulmonary infarction occurred in

7 patients following ligation and in 4 who were not ligated.

THE TREATMENT OF PHLEBOTHROMBOSIS: ANTICOAGULANTS VERSUS FEMORAL VEIN LIGATION. Despite the encouraging results of the prophylactic measures cited above, protection is not afforded in all instances. In addition, the most effective prophylactic measures, anticoagulants and femoral vein ligation, cannot be applied in all postoperative patients. The problem of phlebothrombosis and resultant pulmonary embolism has not, therefore, been eliminated by prophylaxis.

The diagnosis of phlebothrombosis remains a major problem, principally because many fatal embolisms occur without warning signs or symptoms.^{35,38} As mentioned above, two tests^{11,20} designed to show increased coagulability of the blood have been recently described, but neither was sensitive enough to detect or predict the occurrence of thrombosis. At present a positive Homans sign or even slight calf tenderness is regarded as evidence of phlebothrombosis requiring active treatment unless another cause can be clearly shown.

Both anticoagulants and femoral vein ligation have been effective in the treatment of phlebothrombosis. It is the opinion of the author that neither has been shown to be superior to the other on the basis of present data. Advantages of anticoagulants are that an additional operative procedure is not required, the likelihood of venous obstruction in the legs is not increased, and protection is afforded not only in the legs, but throughout the body. In favor of superficial femoral vein ligation is the fact that prompt protection is afforded by a simple, relatively innocuous operative procedure without disturbing so vital a function as the coagulability of the blood.

Recent statements of those with a strong preference for anticoagulants or femoral vein ligation are representative of current differences of opinion. E. V. Allen, Hines, Kvale, and Barker,⁵ leading exponents of anticoagulants, state that they "do not

know of any results from ligation of veins which approach in excellence those derived from our experience with anticoagulants" and that their opinion, "after weighing available evidence, is that the use of anticoagulants is, in general, a much better method of treatment than ligations of veins." Ochsner,⁴⁹ on the other hand, states "that immediate surgical intervention should be undertaken as soon as the diagnosis of phlebothrombosis is made," and "this condition takes precedence, as far as urgency is concerned, over any other case on the service except that of massive hemorrhage." He believes that "although the administration of anticoagulants will prevent the formation of new thrombi it will in no way prevent the detachment of those thrombi which are already in existence" and that "to deny a patient with phlebothrombosis the advantage of the thrombectomy or ligation is hazardous because of the likelihood that detachment of the thrombus will produce non-fatal infarction or fatal embolism." Homans,⁵¹ who introduced femoral ligation in this country, states that it is his "impression, at the moment, that today's tendency is toward increased use of the anticoagulant drugs."

An accurate appraisal of the value and appropriate use of anticoagulants and femoral ligation is not possible at present. Since death from pulmonary embolism occurs only once following every 1000 operations, the accumulation of significant statistical data concerning any method of prophylaxis or treatment will require many more years of careful study.

LIGATION AT VARIOUS LEVELS. From his extensive experience Allen² has concluded that bilateral ligation of the superficial femoral vein is to be preferred for prophylaxis and treatment, and this level has been generally adopted. Recent anatomic studies show that complete protection may not be afforded at this level,⁵² and there are some who now advocate common femoral ligation¹⁶ although such ligations have been followed by serious

venous insufficiency in some instances.^{19,29} When the thrombotic process has extended proximal to the femoral veins, ligation of the iliac veins and vena cava has been performed in relatively large series.^{28,45,56} Iliac and caval ligations are major operative procedures, requiring spinal or general anesthesia. Allen³ and Homans⁵¹ believe these operations have been overdone.

THROMBOPHLEBITIS. Paravertebral procaine block of the lumbar sympathetic ganglia for full-blown acute thrombophlebitis, as suggested by Leriche and Jung⁴² and Ochsner and De Bakey,⁵² has become an established and widely practiced procedure. Some question whether it is more effective in most instances than other, simpler measures which produce vasodilatation and they make the point that it does not prevent pulmonary embolism.^{4,21} Jorpes⁵³ has reviewed the large amount of evidence that heparin is effective in relieving the signs and symptoms of acute thrombophlebitis and in shortening the course of the disease. There is recent evidence that ligation of the femoral and saphenous veins may be helpful in chronic thrombophlebitis (chronic venous insufficiency) by eliminating the stagnant column of blood in the valveless, incompetent veins.^{14,15,50}

PULMONARY EMBOLISM. De Takats and Fowler²¹ believe the mortality of pulmonary embolism may be reduced by the prompt use of atropine and papaverine to reduce vasospasm and bronchospasm. The effectiveness of heparin given intravenously immediately after pulmonary embolism has been well shown by Murray.⁴⁷ In 149 heparinized patients, many of whom appeared to be *in extremis*, there were no deaths, whereas in a control series death occurred in 20%.

Summary. The thrombo-embolism problem as it exists today has been presented. Current trends in prophylaxis and treatment have been reviewed. It is evident that progress has been and is being made in lowering the morbidity and mortality of this disease.

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OPHTHALMOLOGY

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VISUAL HALLUCINATIONS

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As presented in the usual textbook on organic neurology or neuro-ophthalmology, the subject of visual hallucinations seems relatively simple. Thus, Rea¹¹ states that visual hallucinations may occur in the blind field in cases of hemianopsia which must not be mistaken for the visual hallucinations of insanity and which are due probably to irritation of the visual memory center. He states further that the hallucinations due to tumor of the temporal lobe consist of definite images of people, animals or scenes, while those due to lesions in the occipital lobe consist of flashes of light, sparks and the like. According to Weinberger and Grant,¹⁶ similar statements are made by Jelliffe and White, Brain, Brain and Strauss, Wechsler, Grinker, and Purves-Stewart.

However, if one reads further into original articles and individual case reports, the subject becomes much more complex and extremely confusing. Thus, in discussing a single type of hallucination, the lilliputian, Savitsky and Tarachow¹³ state that the occurrence has been reported in measles, erysipelas, typhoid fever; during the convalescent stage of cholera, chorea and sepsis; in acute and chronic alcoholism; in intoxications with cocaine, hashish, hyoscin, caffeine, atropine, chloral and ether; in general paresis; during the oculogyric crises of chronic encephalitis; in association with tumors of the parietotemporal and temporosphenoidal lobes; in association with hemianopic field defects due to

vascular lesions in the occipital lobe; in the very aged; in cerebral arteriosclerosis; in hypnagogic states; in association with blindness secondary to cataract, exudative choroiditis, optic atrophy from acetylsan, tobacco-alcohol amblyopia, choriorinitis; in schizophrenia; in epileptic auræ; in hysteria; and following spinal anesthesia.

It seems obvious, therefore, that the mere occurrence of visual hallucinations of any given type does not furnish any clue to the nature of the process giving rise to the hallucinations. It is true that estimation of the significance of any given hallucination will depend somewhat at least on the individual interpretation of the nature and origin of hallucinations in general. However, Nielsen's¹⁰ statement on the diagnostic value of hallucinations seems to be logical. He says: "Inasmuch as hallucinations are merely activity in the cerebral cortical areas of recall their occurrence in a given case must be analyzed as to physical, chemical, toxic, volitional or subconsciously motivated origin or purpose. They do not of necessity have any psychotic significance even when accompanied by delusions of their reality." The assumption that, in organic disease of the brain, direct involvement of a particular segment of the cortex is necessary to invoke a particular type of hallucination would seem to be rather an oversimplification.

Some of the confusion regarding visual

hallucinations may arise from the varying types of spontaneous visual phenomena which may at times be considered as hallucinations. Weinberger and Grant¹⁶ think that the most acceptable definition of an hallucination is that given by Dorland, "the perception of an object or phenomenon which has no external existence." Allen² states that an image which is at the same time automatic and exteriorized is a sensory hallucination, while an image that is only automatic is a psychic hallucination. Nielsen¹⁰ calls an erroneous interpretation of an actual sensation an illusion. Grant⁵ thinks that in visual illusion the visual system supplies false information about an object to consciousness. He includes in the "visual system" the retina and its cortical projections and also "the cerebral organizations whose function is to give immediate meaning to things seen." Grant⁵ differentiates further sensory illusions, which arise from "the activities of the retina and its cortical projection," and perceptual illusions in which "while the sensory data are valid, the aroused memory associates err by falsely interpreting the stimulation." Some so-called "hallucinations" are doubtless "illusions." Included also in the general conception of hallucinations are visual phenomena such as the scintillating scotoma of migraine, the aura of epilepsy, prolonged or vivid after-images, and entoptic phenomena. Thus Maelay and Guttmann⁹ think that the hallucinations induced by mesaline intoxication have an initial physiologic origin in an entoptic phenomenon, visibility of the capillaries of the choroid. In their opinion, the fact of hallucinating and some formal characters of hallucinations are so similar to physiologic and pathologic phenomena that they can be assumed to be physiologic in origin, but the content of the hallucination is determined by psychologic experiences.

In discussing the mode of origin of visual hallucinations, Johnson⁷ mentions the ideas or theories of 4 authors. Hughlings Jackson hypothesized a visual ideation center from which the sensory discharges

might occur similar to the motor discharges of epilepsy. Jackson thought that stimuli for the discharge of these visual hallucinations might come not only from involvement of the cortical center itself but through the association tracts from a remote lesion. Henschen thought that all visual hallucinations originated in the occipital cortex. Jolly and Pick thought that visual hallucinations had their origin in the optic tracts and Pick added in the geniculate bodies and optic thalamus. It is of interest in this connection that Cutting⁴ believes that the underlying mechanism of dreams and hallucinations is similar and involves a return to a primitive "thalamic" way of thinking. According to Johnson,⁷ Foster Kennedy believes that irritation of the occipital lobe produces simple or crude hallucinations and that irritation of the temporal lobe causes complex hallucinations. Kennedy writes: "Every individual, in his ascent from embryonic to adult life, passes through the stages through which the race has passed. The lower animals make their chief intellectual contact with their environment by means of the hippocampal lobes, which in man are relatively small and unimportant. It may well be that these areas subserve in man early intellectual functions which in later life are carried on by some higher mechanism. If this theory is true, then one may regard these apparitions as involuntary resuscitations of early, perhaps infantile, memory patterns."

The concept of visual hallucinations as revisualizations is supported by Nielsen¹⁰ and by Allen.² According to Nielsen,¹⁰ McDougall classifies hallucinations as representative, constructive and creative. Representative hallucinations are vivid revisualizations or exceedingly clear recall, whether voluntarily or involuntarily produced. Constructive hallucinations consist of aggregates or conglomerations of elements formerly seen. Nielsen¹⁰ does not agree that there can be creative hallucinations, new concepts made out of nothing. He states: "Hallucinations are the result of voluntary or involuntary

activity in the neuronal cerebral cortical system of recall. One experiences in hallucinations only what has been previously perceived through the senses. All hallucinations belong in the category of McDougall's representative or constructive hallucinations; creative hallucinations do not occur." Allen² speaks of the so-called "visuals" who are able to visualize scenes and memory patterns. He mentions, possibly as a transition to visual hallucinations, eidetic images which are neither after-images nor ordinary visual images but a special kind of visual memories which are projected into space as positive images with the original details and colors.

Weinberger and Grant¹⁶ state: "Visual memory and previous visual experience are the *sine qua non* of any visual hallucination. It is well known that congenitally blind children do not have visual hallucinations, even in delirium, although they have auditory and kinesthetic hallucinations." They think that the opticovisual pathways function along the same lines as the general sensory systems and that excitations arising at any point from the retina to the brain give rise to a visual perception through fusion in the brain of purely sensory presentations with psychic factors. They explain the occurrence of simple and complex hallucinations in different individuals under like circumstances by the variability of the image-making function of the mind. "For persons having a high degree of visual imagery, the sensory presentations produced by the abnormal stimulation of the neuro-optic apparatus, such as occurs in association with irritations of the optic nerves, are projected as rich and elaborate images. For those with a poor degree of visual imagery or absence of it, the visual images are simple and relatively 'crude.'" As a result of experience, visual perceptions are projected as if they came from the outside world so that even the blind "see" the hallucinations. Weinberger and Grant conclude, "The principles of cerebral localization cannot be applied to explain highly complex intellectual syntheses, which re-

quire on the face of it the integration of the entire brain."

On the basis of electrical stimulation experiments, it would appear that the source of all visual hallucinations should be in the occipital lobe or at most in the occipital and parietal lobes. According to Lyle,⁸ stimulation of the striate area (Brodman's area 17) produces flashes of light. "When the occipital pole is stimulated, the light is projected before the patient. If the upper or lower calcarine lips are stimulated, the flashes are in the lower or upper fields respectively, corresponding with the fiber projections. Hallucinations, especially of light and color or simple and stationary objects, may be induced by irritation of area 18. More complex hallucinations are found with involvement of area 19." Lyle⁸ states further that the chief function of area 19 is that of revisualization and that the faculties of recognition and revisualization which are separated in areas 18 and 19 are combined in area 39 (the angular gyrus). According to Johnson,⁷ Ferrier believed that the cortex of the angular gyrus is the dominant area of the higher visual center. Brodman's areas 17 and 18 would seem to lie entirely within the occipital lobe, area 19 partially in the occipital and partially in the parietal lobe, and area 39 in the parietal lobe. In agreement with these ideas, Lyle⁸ tends to think that the visual hallucinations associated with tumors of the temporal lobe are caused by secondary involvement of the visuopsychic areas (39 and 19). Lyle⁸ brings up the question of the part played by cerebral dominance in the origin or occurrence of visual hallucinations when he says in reference to injuries of the occipital lobe, "On the major side, which is usually the left, irritation may result in visual hallucinations" and, in reference to tumors of the lower part of the parietal lobe, "If the lesion is on the left side, visual, and, by extension, auditory hallucinations may be present." In this connection, it is of interest that Akelaitis¹ studied the visual functions in 6 epileptics following complete section of

the corpus callosum and concluded that there was no dominance in either cerebral hemisphere for the functions of absolute or relative visual orientation, for absolute or relative discrimination of size, or for recognition of colors, objects or letters. Lyle expresses the opinion that the majority of visual hallucinations, aside from flashes of light, arise from involvements of Brodman's areas 18, 19 and 39. He says, "Visual hallucinations are occasionally described in lesions elsewhere, especially at the anterior tip of the temporal lobe and in the brain stem." In the latter connection, he refers to "the production of visual hallucinations from tumors of the tegmentum of the midbrain, the 'Hallucino-se pedunculaire of L'hermitte,' which is probably produced by the involvement of some of the sympathetic sleep-controlling centers in the hypothalamus adjacent to the midbrain."

In 1933, Johnson⁷ published an extensive review of visual hallucinations accompanying organic lesions of the brain and included an excellent bibliography. He reported 5 additional cases of his own. In 1 patient with a meningioma under the right temporal lobe, the hallucinations were complex but not lateralized, although a left homonymous hemianopsia was present. A patient with a tumor involving the left parieto-occipital lobe had complex visual hallucinations, again not lateralized although a right homonymous hemianopsia was present. A patient with a gunshot injury to the right occipital lobe had simple hallucinations lateralized to the left side and an associated left homonymous hemianopsia. A patient with an astrocytoma in the right cerebellar lobe had complex visual hallucinations which were not lateralized, in association with an optic atrophy and bitemporal hemianopsia which Johnson thought might be due to pressure on the inferior surface of the occipital lobes. A patient with a tumor involving both frontal lobes had normal fields of vision but had complex visual hallucinations lateralized to both temporal fields which Johnson⁷ thought might be due to pressure

irritation of the chiasm. Among Johnson's conclusions from his study were: "Visual hallucinations are elaborated in the higher visual centers in the occipital cortex;" "the production of visual hallucinations presupposes a partially or wholly intact visuopsychic or visuosensory area;" "an irritation of any part of the visual pathway may, under certain pathologic conditions, stimulate the higher visual centers to an elaboration of visual hallucinations;" "complex visual hallucinations . . . are projections of previously stored memory pictures;" "visual hallucinations of a complex type . . . point strongly to an implication of the visual pathway by a lesion in the temporal lobe;" "crude visual hallucinations suggest an implication of the visual conduction tracts or higher visual centers in the occipital lobe;" "as to the lateralizing value of visual hallucinations, a careful study of reported cases reveals that there is none, except that when the hallucinations are projected in a blind homonymous field it is a confirmatory sign that the lesion is located in the contralateral hemisphere."

Johnson's⁷ cases illustrated the variations in the types of visual hallucinations and in the location of the lesions responsible for their production. And his conclusions might be said to present with essential adequacy modern ideas on the interpretation and value of visual hallucinations in the topical diagnosis of organic lesions of the brain. It is of interest, however, to review a few series of cases which have been reported since his publication. It might be postulated that greater significance should attach to lateralized than to global hallucinations, and particularly to hallucinations lateralized in a blind field. It would be of interest to know whether the type of a lateralized hallucination is of more localizing significance than the type of a global hallucination. However, in most of the reported series, the information as to lateralization of the hallucinations is not complete enough to warrant the drawing of conclusions. While it is true probably, as stated by Ironside,⁶

that visual hallucinations of hemianopic distribution are more commonly associated with gross intracranial lesions and visual hallucinations of more global distribution occur more commonly in toxic states, yet even among the hallucinations associated with intracranial tumors, the global seem to outnumber the lateralized hallucinations. Thus, Sanford and Bair¹² state that 22 among 211 patients who had tumors involving the temporal lobe gave a history of visual hallucinations. The hallucinations were lateralized to the blind half of the field in only 2 patients. In the rest of the cases, the visions appeared in the seeing part of the field or oscillated back and forth from the seeing to the blind part. In Sanford and Bair's¹² series, there was no essential difference in type between the hallucinations occurring in association with lesions involving the temporal lobe and those in lesions of the occipital lobe. Of 211 patients with tumors of the temporal lobe, 11 had formed hallucinations and 11 unformed; 2 of 45 patients with tumors of the occipital lobe had formed hallucinations and 2 unformed.

In reviewing a series of 100 cases with visual hallucinations among a group of 800 verified intracranial tumors, Cairns³ listed 10 as being associated with tumors of the occipital lobe. He stated that visual hallucinations of hemianopic distribution in the form of flashes of light or shadow might be the first or an early symptom of tumors in the occipital lobe. In 11 patients with tumors of the parietal lobe, simple visual hallucinations occurred followed by a sensorimotor epileptic discharge. In 21 cases with tumors of the temporal lobe, the hallucinations were more complex in type and were associated with a variety of other sensory impressions. In 16 patients with tumors of the frontal lobe, visual hallucinations were experienced which did not differ in character or clearness from those associated with lesions in other parts of the brain. Cairns³ stated that the localization of the hallucinations experienced by patients with pituitary or suprapituitary tumors did not

correspond with the defects in the visual fields. He thought that visual hallucinations might occur with tumors involving any part of the cerebral cortex, the optic thalamus, or the optic chiasm, and that there must be "a wide system of neurons, stimulation of any part of which might set up hallucinations."

The figures given for the occurrence of visual hallucinations by Tarachow¹⁴ in his review of 458 cases of supratentorial tumors are somewhat difficult to evaluate. Apparently, unformed hallucinations were complained of by 23 patients with lesions variously placed in the frontal, temporal, parietal and occipital lobes, in the thalamus, third ventricle and pituitary. Fourteen lesions causing formed hallucinations were distributed among the frontal, temporal, parietal and occipital lobes and the optic chiasm. Among the cases in which the tumor was confined to the frontal lobe, formed hallucinations occurred in 1 and unformed in 2; in tumors confined to the temporal lobe, the hallucinations were formed in 2 and unformed in 2; in tumors confined to the parietal lobe, the hallucinations were formed in 1 and unformed in 2; and in tumors confined to the occipital lobe, the hallucinations were formed in 2 and unformed in 2. Tarachow¹⁴ stated that pure occipital lobe lesions gave rise to visual hallucinations alone, not associated with other forms of hallucinations; but visual hallucinations, both formed and unformed, could occur in association with lesions spread almost equally throughout all the lobes of the brain.

The figures given by Allen² likewise are rather difficult to interpret. It would appear, however, that he encountered formed visual hallucinations in association with tumors in the frontal, temporal and occipital lobes, but not in the parietal lobe. Unformed visual hallucinations were encountered in tumors involving any one of the frontal, temporal, parietal or occipital lobes. Allen stated that, in vascular lesions in the occipital lobe, spontaneous visual phenomena, more often formed than unformed, might appear in the contra-

lateral hemianopic field sometimes for a short time just before the onset of the hemianopsia, often while the hemianopsia was present, and sometimes during the disappearance of the hemianopsia.

Weinberger and Grant¹⁶ described and discussed the visual hallucinations observed in 12 patients with adenomas of the pituitary body and 4 patients with tumors of the hypophyseal duct. In 3 of the cases, the hallucinations were simple and not lateralized; in 2 cases, they were simple and lateralized; in 8 cases, they were complex and not lateralized; in 2 cases, they were complex and lateralized. In 1 patient, simple hallucinations were seen in front of the blind right eye only in association with complex hallucinations of global distribution. Two of the patients in whom the hallucinations were lateralized were totally blind. In only 1 case were the hallucinations lateralized to a blind hemianopic field.

It is generally believed that visual hallucinations are more common in association with tumors involving the temporal and occipital lobes than in lesions involving the optic nerves and chiasm. However, Weinberger and Grant¹⁶ collected 22 cases with visual hallucinations among 139 pituitary adenomas (15.8%) and 6 among 84 tumors of the hypophyseal duct (7.1%). Sanford and Bair¹² reported visual hallucinations in 10.4% of 211 patients with temporal lobe tumors and in 8.9% of 45 patients with occipital lobe tumors.

Weinberger and Grant¹⁶ think that all visual hallucinations are basically identical and that, therefore, the type of the hallucination is of no localizing significance. They stated: "The distinction has been made between the composition of a crude, or simple, hallucination and the composition of a complex, or formed, hallucination without the difference being entirely clear. The 2 have been thought of as comprising separate order of phenomena, but this attitude is not compatible with psychologic facts. The simple or crude hallucinations are recognized by the patient as being a 'thing' just as the more elaborate images

are. Regardless of whether an image is a simple 'thing,' it nonetheless possesses enough characteristics to be recognizable and nameable. . . . Between the simplest type of visual image and the most elaborate there are imperceptible gradations. . . . From this point of view there are really no crude or complex images but merely hallucinations of different things. . . . It seems to matter but little at what point in the neuro-optic apparatus the stimulus is given. The final perception does not correspond to the immediate stimulus but conforms to the background provided by experience."

On the basis of their review of the literature, Weinberger and Grant¹⁶ state: "It appears, therefore, that when the cases in the literature are scrutinized, the categorical opinions that distinctive types of hallucinations are peculiar to either the temporal or the occipital lobe become highly doubtful." These authors conclude from their studies that visual hallucinations in themselves have no localizing value whatever in focal diagnosis, that they may be provoked by lesions at any level of the neuro-optic apparatus, and that they are not due to local cortical excitability but are psychologic phenomena involving the total integrative activities of the mind.

An unbiased survey of the material at hand would certainly seem to justify the conclusion that it is unwise to attribute too much localizing significance to the type of visual hallucination present in any given case of organic disease of the brain. And yet it is very difficult to rid the clinician of his impression that complex visual hallucinations, particularly if lateralized, furnish supportive evidence that the lesion is in the temporal lobe. In the most recently published book on Neuro-ophthalmology, Walsh¹⁵ discusses the subject of visual hallucinations with especial attention to the report of Weinberger and Grant.¹⁶ In reference to the frequency of hallucinations occurring in association with lesions affecting the optic nerves and chiasm, Walsh¹⁵ says: "We have not examined our tumor material from this

standpoint, but I should be greatly surprised if other than in temporal and occipital lobe involvements there were anything like the number of cases of visual hallucinations that these observers described." He recognizes the occurrence of visual hallucinations in individuals suffering from purely ocular disorders and states: "Such visual hallucinations if they take the form of flashing lights either white or colored are properly attributed to retinal irritation, since individuals with separation of the retina commonly make complaints regarding such sensations of light but do not, so far as I am aware, complain of complex visual imagery." Walsh¹⁵

thinks that the visual hallucinations to postoperative cataract patients are psychologic and similar to the visual phenomena of nightmares. In the conclusion of his discussion, Walsh¹⁵ states: "I am unwilling to accept the conclusions of Weinberger and Grant¹⁶ *in toto*. There are too many cases which support the proposition that formed hallucinations may arise as the result of temporal lobe involvement and that unformed ones may originate in involvements of the occipital lobe to accept new evidence without its being further substantiated." And there the matter must rest.

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PHYSIOLOGY

PROCEEDINGS OF

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SESSION OF DECEMBER 16, 1947

Electrical Properties of Living Tissues.

HERMANN SCHWAN, DR. RER. NAT., DR. HABIL (Kaiser-Wilhelm Institut Biophys., Frankfurt/Main, and AMEL, Phila. Naval Base). The dielectric constant, ϵ , and conductivity, γ , of living tissues can be measured for 6 hours *in vitro*. These constants determine the convection and displacement currents. Dispersions of ϵ and γ with frequency have been demonstrated in 3 frequency ranges: between 30,000 and 300 kc. from 1935 to 1938, at lower frequencies in 1938, and above 300,000 kc. more recently. Inhomogeneous structure or polar orientation of molecules could cause each of these dispersions. The relationships between ϵ and γ and frequency alone do not elucidate the phenomena. At frequencies near 14 ke., the author has found that ϵ of erythrocyte suspension is independent of temperature, showing that polar orientation is not responsible for dispersion in the 30,000 to 300 ke. range. Dispersion of ϵ in the lowest frequency range is greater at higher values of γ , which is itself not dispersed. The author ascribes these effects to polarization at the electrode solution interface. Scanty measurements by Malov, Paetzold and Gsell at very high frequencies have now been extended over a wider range, 160 to 830 mc., by new techniques. Dispersion of ϵ and γ starts at about 600 mc., and is due to polar organization in the test solutions.

Such measurements are fundamental in diathermy. The heat developed in fat decreases more than that developed in muscle or other tissues at higher frequencies. However, penetration decreases at diminishing wave lengths. The techniques mentioned above indicate optimal wave lengths for diathermy in the decimeter range.

Other applications of electrical measuring techniques include determination of erythrocyte volume (hematocrit) with low frequencies, erythrocyte size distribution with extremely low or high frequencies, and erythrocyte wall thickness. Another new electrical technique, superior to the Westergren method, determines sedimentation rate precisely and rapidly.

A New Method for the Extraction of Tissue Proteins, With Particular Reference to Muscle. WILLIAM R. AMBERSON, PH.D., RUBERT S. ANDERSON, PH.D., BETTY CHINN, and T. ERDÖS, M.D. (Dept. of Physiology, Univ. of Maryland, and Institute of Physical Chemistry, Univ. of Uppsala). Myogen and myosin may be extracted from whole muscle, without cutting or grinding. The tissues are placed in closed vessels and frozen in CO₂ snow. Extracting solutions are then poured over them and extraction proceeds at 0° C.

Distilled water extracts myogen from whole muscles, up to 2% of the net weight after 5 days. No myosin is extracted and the solutions remain low in viscosity. Electrophoretic diagrams of white muscle extracts, after dialysis, show 2 components, 1 large and slow, the other small and fast. Red muscle extracts show, in addition, a myoglobin peak, of intermediate velocity.

Salt solutions, such as 0.4 mg. K phosphate buffer at pH 7.6, which readily extract myosin from minced or sliced muscles, are not able, for many days, to extract this protein from whole muscles. Such salt solutions mobilize a larger yield of myogen, up to 4% of the wet weight, but the viscosity remains low. The electrophoretic diagrams are similar to those obtained from distilled water extracts.

When pyrophosphate ($\text{Na}_4\text{P}_2\text{O}_7$, 500 mg. %) is added to 0.4 mg. K phosphate buffer, the mixture is able to extract a minor percentage of the myosin of whole muscles, up to 1% of the wet weight, in addition to the myogen. Such extracts develop considerable viscosity. The electrophoretic pattern now shows a sharp myosin peak, with velocity somewhat faster than that of myoglobin. Neither actomyosin nor actin appears. The presence of myosin is also demonstrated by sharp peaks in the ultracentrifuge sedimentation diagrams. The myosin may be separated from the other protein by electrophoretic fractionation.

The Influence of Non-electrolytes on the Ionic Equilibria of Cells. M. H. JACOBS, PH.D. (Dept. of Physiology, Univ. of Penna.). It was shown by Donnan that the presence of non-diffusible ions may profoundly influence the distribution of diffusible ions in a heterogeneous system. It is not so well known that non-diffusible non-electrolytes may have a similar effect, provided that the system in question is subject to osmotic volume changes, as is almost always the case with animal cells.

By the use of principles recently discussed elsewhere (*J. Cell. Comp. Physiol.*, 30, 79, 1947) equations have been derived for the determination of the theoretical ionic and osmotic equilibria of a cell exposed to any desired mixture of an elec-

trolyte such as NaCl and a non-penetrating non-electrolyte such as sucrose. These equations, when applied to a hypothetical cell having the properties and the approximate composition of the mammalian erythrocyte, indicate that internal pH changes of very considerable magnitude might be produced by merely varying the proportion in the external solution of the 2 entirely neutral solutes in question.

The equations also permit further predictions, which have been confirmed experimentally, concerning the character of the volume changes produced by the addition of different quantities of NaCl to suspensions in a solution of sucrose of (a) normal, (b) ion-impermeable, and (c) cation-permeable erythrocytes. (The condition of ion-impermeability can be approximately realized by treatment of the cells with dilute tannic acid; that of cation-permeability by a short exposure to butyl alcohol.) With increasing additions of NaCl the ion-impermeable cells at equilibrium show only shrinkage, the cation-permeable cells only swelling, while the normal cells show swelling at very low concentrations of salt, a maximum volume and a return to the original volume at moderate concentrations, and increasing shrinkage at higher concentrations. The observed positions of maximum volume and of no volume change are in reasonably good agreement with those calculated theoretically.

BOOK REVIEWS AND NOTICES

SURGICAL DISORDERS OF THE CHEST. By J. K. DONALDSON, M.D., F.A.C.S., Assoc. Prof. of Surgery, Univ. of Arkansas School of Medicine, etc. 2nd ed. Pp. 485; 146 ills., 2 color plates. Phila.: Lea & Febiger, 1947. Price, \$8.50.

THE first edition of this book was widely accepted as being among the best of the few available texts dealing with surgical diseases of the chest. In this edition most of the material has been revised and much rewritten; 120 pages and 22 illustrations have been added. Recently introduced operations on the great vessels are described, and advances in thoracic surgery during World War II are discussed, with emphasis on hemothorax and decortication of the lung. The book is not intended for specialists in thoracic surgery; for students, general practitioners, and surgeons without special training in thoracic surgery, however, it is a valuable source of clear and accurate information about the pathogenesis, diagnosis and treatment of surgical chest diseases. References to articles appearing within recent months are included, and in general the book is probably as up-to-date as possible in this rapidly expanding field. C. K.

DOCTOR FREUD. An Analysis and a Warning. By EMIL LUDWIG. Pp. 317. New York: Helman, Williams & Co., 1947. Price, \$3.00.

It is said of this book that in Europe it is either damned or praised to the skies. In America it will probably rouse a considerable interest. It will be seen that the author's spear is pointed more at Freud's philosophy than at his psychology, and at that philosophy as it spreads into education, sociology, economics and religion. But Emil Ludwig, the biographer of Napoleon and Goethe, when he objects to the historical analysis of these men by Freud and his disciples, is on his own ground. His comments on Freud's life are also within his own boundaries. Most Americans will think that his ventures into psychology and psychiatry leave him far from home. E. B.

ANDREAS VESALIUS BRUXELLENSIS: THE BLOODLETTING LETTER OF 1539. An Annotated Translation and Study of the Evolution of Vesalius' Scientific Development. By JOHN B. DE C. M. SAUNDERS, F.R.C.S. (EDIN.), and CHARLES DONALD O'MALLEY. Pp. 94. New York: Henry Schuman, 1947. Price, \$5.00.

Its introduction expanded by some 16 pages, and with the addition of an index, this is otherwise a reprint of 1 of the 28 contributions to the *Studies and Essays in the History of Science and Learning Offered in Homage to George Sarton*, published by the house of Henry Schuman; at \$12, somewhat earlier in the same year. No statement of this relationship appears in the publication under review.

As the first complete work of Vesalius to appear in the English language, the publication is of exceptional interest, and even more deeply gratifying by virtue of the authority and scholarship the translator-editors have brought to their task. One can therefore only regret the more that such excelling inducements to the cultivation of an interest in medical history continue, at least in our country, to be subservient to the special interests of the bibliophile. It seems a pity that they are kept out of range of the modestly endowed library and individual that is tempted to feast on such stimulating fare but cannot afford it.

W. McD.

THE DEVELOPMENT OF MODERN MEDICINE. By RICHARD HARRISON SHRYOCK, PH.D., Professor of History, Univ. of Pennsylvania. 2nd Ed. Pp. 457; 10 ills. New York: Alfred A. Knopf, 1947. Price, \$5.00.

THIS edition of a well-known and valuable treatise on the history of medicine, which was first published in 1936, maintains its own high standard. The book is unique among medical histories for its emphasis on public health and for its integration of medical and social history. As a general historian experienced in the study of social progress, Dr. Shryock has broadened the base of medi-

cal history. This 2nd edition is particularly valuable for its account of the powerful movements of the last decade directed toward group insurance against illness and lowered cost of medical care. The parts played by organized labor, industry and the Federal Government during the Roosevelt administration are well covered. The controversy between organized medicine and the proponents of new procedures in medical practice is well presented in an unbiased manner that loses nothing of interest in its careful preservation of an objective point of view.

Emphasis is placed on the progressive development of coordinated research, both in the basic sciences and the application of medical discoveries to improvement in clinical practice and public health. Attention is called to the changes in the age distribution of the population brought about by success in the prevention and therapy of infectious disease, and stress is laid on the incidence of chronic disease, particularly of a degenerative character, and its implications in a society with an enlightened sense of responsibility for human welfare. The chapter on mental disease has been brought up to date with reference to the new appreciation by the medical profession of psychosomatic medicine, and the great frequency of psychoneurotic disorder, illustrated startlingly in the medical experience of the late war.

The final chapter on Some Contemporary Questions points out the leads that recent medical advance has given for future medical progress. It is quite in keeping with the spirit of an optimistic historian, who looks upon medicine as a great social science.

E. L.

THE FOOT AND THE ANKLE. By PHILLIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern Univ. Medical School. 3rd Ed. Pp. 347; 389 ill. Phila.: Lea & Febiger, 1947. Price, \$11.00.

In this expanded edition, the author's revisions incorporate recent information. The foot and ankle are again considered as a unit integrated with the whole, so that many conditions which only incidentally concern these structures are comprehensively discussed.

The consideration of many different con-

ditions is sufficient in detail to make the book valuable as a reference. On the other hand it is easily readable as a textbook for the specialty student. The chapters on fractures, dislocations, and injuries have been enlarged. More space is devoted to vascular disturbances, and the author's medical experiences of the last war are included.

In this edition the author frequently employs outlines set off from the text to emphasize important material. The many drawings and photographs are of high standard and enhance the text.

P. C.

AMABLE AUTOCRAT: A BIOGRAPHY OF DR. OLIVER WENDELL HOLMES. By ELEANOR M. TILTON. Pp. 470; 9 ill. New York: Henry Schuman, 1947. Price, \$5.00.

Obviously biographies should be informative. This one is. Scrupulous labor went into its composition, along with an admirable determination to present Dr. Holmes as a whole. At times Miss Tilton seems almost to achieve the aim of balance defined by Lewis Carroll as crying "Riddleham" when uncertain whether to say "Richard" or "William." Dr. Holmes himself, however, irrepressibly escapes his biographer's dispassion and shows, among other things, that amiability is not the preponderant qualifying ingredient of his great yet uncreative literary abilities.

Miss Tilton praises a "discriminating" review of 3 essays by Dr. Holmes, written by Gerhard for *THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES* (22, 163, 1838). This Reviewer hopes she may accord a like adjective to the statement that her book is recommended to everyone interested in physicians or in men of letters.

E. T.

A HANDBOOK ON DISEASES OF CHILDREN, INCLUDING DIETETICS AND THE COMMON FEVERS. By BRUCE WILLIAMSON, M.D. (Edin.), F.R.C.P. (Lond.), Royal Northern Hospital, London. 5th Ed. Pp. 403; 83 figs. Baltimore: Williams & Wilkins, 1947. Price, \$4.50.

This little book presents a brief outline of Pediatrics as seen by one competent and experienced observer. As such, it may be read with pleasure by the Pediatrician for its vivid descriptions and clear readable style. The author gives his own opinions and these are stimulating even when one

disagrees with them. The general practitioner will find much to help him in the brief but lucid descriptions and in the many practical suggestions as to therapy. The photographs are numerous and well chosen. Five editions in 14 years are sufficient indication of its popularity. For the undergraduate student, the book has the faults of any small handbook which covers a large field, and is not recommended. F. H.

A TREATISE ON GONIOSCOPY. By MANUEL URIBE TRONCOSO. Pp. 318; 117 ills., 35 in color. Phila.: F. A. Davis, 1947. Price, \$10.00.

THIS book, by one of the pioneers in this subject, has the weight of authority which only comes from long acquaintance. The first part gives a comparison of the anatomy of the angle of the anterior chamber, in mammalia, from the rodents up to man; and then the microscopic anatomy of the angle in man compared with that seen with the gonioscope. An excellent chapter on the comparative physiology of the aqueous outflow is followed by one on the embryology of the angle by Ida Mann. The rest of the book is a history of the development of gonioscopy, the techniques of gonioscopic examination and a description of the angle of the anterior chamber in various pathologic conditions. It will undoubtedly take time to revise some of our clinical concepts in the light of our newer knowledge of the physiology of the aqueous outflow, but no ophthalmologist can afford to evaluate cases of glaucoma without inquiring into the status of the angle of the chamber. This will undoubtedly become a routine office procedure. This book should be in the hands of every competent ophthalmologist who attempts to treat glaucoma.

F. A.

NUTRITIONAL DISORDERS OF THE NERVOUS SYSTEM. By JOHN D. SPILLANE, B.Sc., M.D. (WALES), M.R.C.P. (LOND.), Assistant Physician and Neurologist, Cardiff Royal Infirmary. Foreword by GEORGE RIBBOCH, M.D., F.R.C.P. Pp. 280; 103 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$5.00.

THE author presents a comprehensive and exceedingly well-documented account of the general effects of malnutrition in humans. The material is well organized and is pre-

sented in a readable, clear, critical and systematic manner. Two chapters are devoted to the nutritional encephalopathies, 1 chapter each to degenerative lesions of the spinal cord and to polyneuritis. The history, chemistry and pharmacology of the known vitamins and the clinical pictures of pellagra and beriberi are fully dealt with. Of special interest are the well-illustrated chapters giving the author's personal experience among refugees and prisoners of war. Our present incomplete understanding of all the factors which determine the incidence of nutritional disease, and the unpredictability of successful therapy is acknowledged, and the possible rôles of quantitative as well as qualitative deficiencies is discussed. The book is attractively bound and well illustrated. J. L.

CLINICAL NEURO-OPHTHALMOLOGY. By F. B. WALSH, M.D., F.R.C.S. (EDIN.), Associate Professor of Ophthalmology, The John Hopkins Univ. Pp. 1532; 384 figs. Baltimore: Williams & Wilkins, 1947. Price, \$15.00.

THIS is a monumental work. It represents the accumulated experience of years of careful observation of patients and a thorough study of the literature on neuro-ophthalmology. Dr. Walsh is well known for his original contributions to this subject, and his book far surpasses any in English that has attempted to cover the field.

The 17 chapters are as follows: (1) The visual pathways. Diagnosis of lesions situated at different levels. (2) Other cranial nerves. Topical diagnosis. (3) The autonomic system. (4) The pupil; normal and abnormal accommodation. (5) The eyelids and extraocular muscles. (6) Papilledema, optic neuritis, optic atrophy. (7) Congenital and development abnormalities and disease of the eyes and central nervous system. (8) Infection and parasitic invasions of the nervous system and their ocular signs, including an outline of nervous system and ocular syphilis. (9) Heredofamilial and degenerative diseases. (10) Toxic and Metabolic diseases. (11) Disorders of muscles. (12) Vascular lesions and circulatory disorders of the nervous system; ocular signs. (13) Ocular and intracranial tumors and related conditions. (14) Injuries by physical agents; ocular signs. (15) Epilepsy; migraine, and other paroxysmal disorders. (16) The ocular signs

of hysteria; malingering, and traumatic neurosis. The psychiatric aspect of ocular disorders. (17) Drugs, poisons, and toxic amblyopias.

This book will be a welcome addition to the library of every ophthalmologist and neurologist and neurosurgeon. F. A.

TOMORROW'S FOOD—THE COMING REVOLUTION IN NUTRITION. By JAMES RORTY and N. PHILIP NORMAN, M.D. Pp. 258. New York: Prentice-Hall, 1947. Price, \$3.50.

THE authors of this volume, a journalist and a physician, join forces to present an intriguing story addressed to the lay reader. They are concerned not so much with the quantity of food available to us, but rather with the quality as measured in the units of a balanced diet. They cite the growing record of physical ills that may be attributed in part to imbalanced nutrition. This imbalance can arise from the use of products produced on depleted soils, but more particularly from the use of "devitalized" food-stuffs. Our food habits have been so developed that we accept, in preference, highly milled cereal grain products and "pure" sucrose as major components of our daily food. "Enrichment" programs are not accepted as the way to improve the situation.

The food problem is not a simple one, being composed of nutritional, economic, social and political elements. The authors urge that the important discoveries of the soil scientist and the plant breeder should be utilized to increase the yield of foodstuffs, and also that improved methods of food processing be more generally adopted. Finally, that more efficient and less wasteful methods of distribution are necessary. Only when all phases of the problem are integrated to the benefit of the consumers shall we enjoy the optimum nutrition now denied us.

H. V.

PRACTICAL ANESTHESIA FOR DENTAL AND ORAL SURGERY—LOCAL AND GENERAL. By HARRY M. SELDIN, D.D.S., F.I.C.D., F.I.C.A. Consulting Oral Surgeon, Harlem Hosp., New York City Cancer Institute and Peekskill Hospital. 3d Ed. Pp. 592; 238 ill. Phila.: Lea & Febiger, 1947. Price, \$8.50.

THIS textbook has been revised and expanded in an attempt to keep pace with newer concepts and techniques in anesthesia. In addition to the chapters on nitrous oxide anesthesia, those dealing with intravenous anesthesia and the application of local anesthesia in operative dentistry and root canal therapy have been expanded and rearranged. New illustrations have been added.

Several chapters are devoted to the physiology and pharmacology of inhalation anesthesia and respiration. This effort, though commendable, is marred by numerous errors in basic physiology. For instance, the statements that a decrease in respiratory rate, and even apnea, can be produced by "over-oxygenation;" that the innervation of the carotid body is via the vagus nerve; that "when a normal person assumes the recumbent position, respiration usually becomes slower and deeper due to the irregular distribution of the air in the pulmonary alveoli."

A superficial attempt is made to aid the dentist in evaluating poor risks for anesthesia, but there is no recommendation for the hospitalization of certain poor-risk patients for anesthesia and oral surgery. In fact, the author tacitly decries such a practice when he concludes, on the grounds of some questionable statistics, that office dental anesthesia is safer than hospital anesthesia.

This text should prove of some value to those practising local anesthesia for oral surgery and may be helpful to those interested in various techniques of nitrous oxide anesthesia. The illustrations and charts are splendid.

K. E.

ANESTHETIC METHODS. By GEOFFREY KAYE, ROBERT ORTON and DOUGLAS RENTON. Univ. of Melbourne and the Alfred Hospital, Melbourne. Pp. 706; 188 ill. Melbourne, Australia: W. Ramsey (Surgical) Pty. Ltd., 1946. 50 shillings.

THIS new text is intended to provide more information than is present in manuals, but less than in exhaustive volumes written for specialists in anesthesiology.

Basal, inhalational, intravenous and spinal anesthesia are discussed thoroughly. Local anesthesia is not considered since the authors regard regional techniques as impractical for casual anesthetists. It is unfortunate that such simple methods as

caudal, brachial plexus, and lumbar sympathetic blocks are not described.

The outline on premedication is brief and indefinite. Atropine and scopolamine are recommended for use only prior to administration of irritative vapors and intravenous anesthetics. The chapters concerned with the pharmacology of anesthetic agents are concise and informative. The outstanding features of the book are the large number of excellent diagrams of anesthesia machines and the descriptions of the use of these machines in administration of anesthetics.

The volume can be recommended to all physicians interested in anesthesia. Its conservative viewpoint makes it of value to practitioners who must administer anesthetic agents occasionally.

R. D.

THE LUNG. By WILLIAM SNOW MILLER, M.D., Sc.D., late Emeritus Professor of Anatomy, Univ. of Wisconsin. 2nd Ed. Pp. 222; 168 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$7.50.

THIS classic in anatomy represents a lifetime of painstaking research by an investigator who lived to advanced years. Between the first publication of the volume in 1937 and Miller's death in 1939 he continued to gather material and to study the growing literature critically. Actually, however, the chief items added date from 1932 to 1935, the material of the 1st edition representing largely the results of research up to 1932.

As the review of the 1st edition in this *Journal* stated, "Its greatest value lies in its superb illustrations, because these enable the reader to grasp and understand pulmonary structure in 3 dimensions." The 2nd edition contains 16 more illustrations than the 1st, including 3 color plates, and 33 more references to the literature. The few inferior illustrations of the 1st edition have been replaced by better ones. New text material appears chiefly in 2 chapters. Miller added substantially to his concept of a true epithelial lining of the lung alveoli, through the introduction of sections from pathologic lungs. In the Preface he stated that he had devoted much time to this after the appearance of the 1st edition and found no reason to change his views. He admitted that "some workers think differently."

The second significant addition is in the text on the pleura, in which use is made of

O. Larsell's ultimate discovery of nerve endings in the human pleura, after his initial failure to find them. The highly important chapters on the blood-vessels and lymphatics and on pulmonary lymphoid tissue remain virtually unchanged, as does the short chapter on "key points" with which every student of the lung is now familiar.

The format is similar to that of the 1st edition. The illustrations and printing are slightly sharpened, and in general the press work is excellent.

E. L.

ESSENTIALS OF ENDOCRINOLOGY. By ARTHUR GROLLMAN, Ph.D., M.D., Professor of Medicine and Chairman of the Dept. of Experimental Medicine, The Southwestern Med. Coll.; Attending Physician and Consultant in Endocrinology, The Parkland Hosp., Dallas, Texas. 2nd ed. Pp. 664; 132 ills. Phila.: J. B. Lippincott, 1947. Price, \$10.00.

THIS is in general a sound and well-written outline of endocrinology. Following a basic introductory survey, the text is divided into 5 major parts, dealing respectively with the endocrine organs of the cranial cavity, the branchiogenic, abdominal and reproductive endocrines, and the hormones derived from non-endocrine organs. The style is generally lucid, the approach conservative and the graphs and illustrations well chosen. The anatomic and physiologic factors underlying the clinical disorders of each part of the endocrine system are generally well discussed and properly emphasized, although the section on carbohydrate metabolism might be a little more detailed and less vague. There are a few typographical errors. The page subject headings and the list of therapeutic endocrine preparations on the inside covers are commendable features.

The hypercritical might take exception to some errors of omission. For instance, the malignant potentialities of nodular goiter are inadequately stressed; the discussion of gynecomastia is too sketchy; the important contribution of the Coris on the interaction of insulin and anterior pituitary extract in carbohydrate metabolism is not mentioned; the concept of pseudohypoparathyroidism receives no comment; disturbances of carbohydrate metabolism in patients with hyperfunctioning tumors of the adrenal medulla are not mentioned, and the contraindica-

tions to the testosterone therapy are insufficiently emphasized. More space might have been given to the adaptation syndrome and its implications; and some may question the justification for considering metabolic cranio-pathy as a definite clinical entity. One wonders, also, whether Cushing's syndrome might have been more logically classified as an adrenal disorder than as one of primary pituitary origin. One may seriously doubt the diagnostic value of the response to subcutaneous injections of small doses of epinephrine in suspected functioning tumors of the adrenal medulla. However, despite these relatively minor criticisms this book may be recommended as among the best in its field in the current American literature.

E. R.

COMMON CONTAGIOUS DISEASES. By PHILIP MOEN STIMSON, A.B., M.D., Assoc. Prof. of Clinical Pediatrics, Cornell Univ. Medical College. 4th ed. Pp. 503; 67 ills., 8 plates, 6 in color. Phila.: Lea & Febiger, 1947. Price, \$4.00.

THIS book continues to be a useful exposition of the so-called contagious diseases. The contents have been largely rewritten; a new chapter on the sulfonamides and antibiotics has been added; the chapter on pilio-myelitis is practically new; more illustrations and photomicrographs have been incorporated and the bibliography brought up-to-date. The fact that this text has gone through four editions speaks for itself. Written by a pediatrician, the book omits some diseases that could qualify as contagious diseases, viz.: scabies and pediculosis; erysipelas. Certain aspects of some contagious diseases are also given slight notice. For example, no detailed discussion of cutaneous diphtheria and the pyoderma is included. However, this edition adequately fills a need for the student and practitioner.

H. B.

NEW BOOKS

Clinical Neuro-Ophthalmology. By FRANK B. WALSH, M.D., F.R.C.S. (EDIN.), Assoc. Prof. of Ophthalmology, The Johns Hopkins Univ. Pp. 1532; 384 figs. Balt.: Williams & Wilkins, 1947. Price, \$15.00.

Gonioscopy. By MANUEL URIBE TRONCOSO, M.D., Assist. Clinical Prof. of Ophthalmology, College of Physicians and Surgeons, Columbia Univ. Pp. 318; 117 ills., 35 in color. Phila.: F. A. Davis, 1947. Price, \$10.00.

Dermatology in General Practice. By SIGMUND S. GREENBAUM, B.S., M.D., F.A.C.P., Prof. of Clinical Dermatology and Syphilology, Univ. of Pennsylvania Graduate School of Medicine. Pp. 889; 846 ills., 20 in color. Phila.: F. A. Davis, 1947. Price, \$12.00.

Practical Office Gynecology. By KARL JOHN KARNAKY, M.D., Assist. Prof. of Clinical Gynecology, Baylor Univ. Pp. 261; 113 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$7.50.

Handbook on Fractures. By DUNCAN EVE, JR., M.D., F.A.C.S., Assoc. Prof. of Surgery, Vanderbilt Univ. Pp. 263; 129 ills. St. Louis: C. V. Mosby, 1947. Price, \$5.00.

Jaundice, Its Pathogenesis and Differential Diagnosis. By ELI RODIN MOVITT, M.D. Pp. 261; 22 ills. New York: Oxford Univ. Press, 1947. Price, \$6.50.

Amiable Autocrat: A Biography of Dr. Oliver Wendell Holmes. By ELEANOR M. TILTON, Pp. 470; 9 ills. New York: Henry Schuman, 1947. Price, \$5.00.

Dynamic Aspects of Biochemistry. By ERNEST BALDWIN, B. A., Ph.D., University Lecturer in Biochemistry, formerly Fellow of St. John's College, Cambridge. Pp. 457; 33 figs. New York: The Macmillan Company, 1947. Price, \$4.00.

Calcium and Phosphorus in Foods and Nutrition. By HENRY C. SHERMAN, Mitchell Prof. Emeritus of Chemistry, Columbia Univ. Pp. 176. New York: Columbia University Press, 1947. Price, \$2.75.

400 Years of a Doctor's Life. Collected and Arranged by GEORGE ROSEN, M.D., and BEATE CASPARI-ROSEN, M.D. Pp. 429. New York: Henry Schuman, 1947. Price, \$5.00.

Your Teeth: And How to Keep Them. By JEROME J. MILLER, D.D.S., formerly Assist. Prof. of Oral Surgery, New York Univ. Pp. 232; 44 figs. New York: Lantern Press, 1947. Price, \$3.00.

Physics for the Anæsthetist. By R. R. MACINTOSH, M.A., M.D., F.R.C.S., D.A., Nuffield Prof. of Anæsthetics, Oxford, and WILLIAM W. MUSHIN, M.A., M.B., B.S., D.A. Pp. 235; 431 ills., 152 in color. Springfield, Ill.: Charles C Thomas, 1947. Price, \$7.50.

College Chemistry in Nursing Education. By EDNA CURTISS MORSE, R.N., A.M., Ed.D., Assist. Prof. of Home Economics, Columbia Univ. Pp. 260. New York: The Macmillan Company, 1947. Price, \$4.00.

Nursing in Modern Society. By MARY ELLA CHAYER, R.N., A.M., Assoc. Prof. of Nursing Education, Columbia Univ. Pp. 288. New York: G. P. Putnam's Sons, 1947. Price, \$4.00.

The Oculorotary Muscles. By RICHARD G. SCOBEE, M.D., Instructor in Ophthalmology, Washington Univ. School of Medicine, St. Louis. Pp. 359; 112 figs. St. Louis: C. V. Mosby, 1947. Price, \$8.00.

THIS is a very readable book on the diagnosis and treatment of disturbances of the oculorotary of the eye. The author has an easy and informal style and develops his subject logically and with clarity. He deals with a subject in which there are many controversial points and his dogmatism is justified in the interests of teaching. The chief value of the book is in presenting the author's view on comitant and incomitant squint in children. The book will be of value to all who are interested in ocular muscle anomalies. (F. A.)

Unipolar Lead Electrocardiography. By EMANUEL GOLDBERGER, B.S., M.D., Adjunct Physician, Montefiore Hospital, New York. Pp. 182; 88 ills. Phila.: Lea & Febiger, 1947. Price, \$4.00.

Doctor Freud, an Analysis and a Warning. By EMIL LUDWIG. Pp. 317. New York: Hellman, Williams & Co., 1947. Price, \$3.00.

Ulcer, The Primary Cause of Gastric and Duodenal Ulcer. By DONALD COOK, B.A., M.D. Pp. 187; 27 figs. Chicago: Medical Center Foundation and Fund, 1947. Price, \$5.00.

Blood Derivatives and Substitutes. By CHARLES STANLEY WHITE, M.D., former Prof. of Surgery, George Washington Univ. School of Medicine, and JACOB JOSEPH WEINSTEIN, B.S., M.D. Pp. 484; 190 figs. Balt.: Williams & Wilkins, 1947. Price, \$7.50.

Hypnotherapy, a Survey of the Literature. By MARGARET BRENNAN, Ph.D., Prof. of Psychology, Univ. of Kansas, and MERTON M. GILL, M.D., Assoc. Psychiatrist. The Menninger Foundation Monograph Series No. 5. Pp. 276. New York: International Universities Press, 1947. Price, \$4.50.

THIS is an authoritative book and one that is a valuable contribution to its field. It consists of: a section on hypnotherapy (originally published in 1944 by the Josiah Macy Jr. Foundation); 4 case studies in which hypnotherapy was employed; and an experimental study of "tension systems" in the Lewinian sense. An extensive bibliography is included. (E. B.)

A Primer of Cardiology. By GEORGE E. BURCH, M.D., F.A.C.P., Assoc. Prof. of Medicine, Tulane Univ., and PAUL REASER, M.D., Instructor in Medicine. Pp. 272; 203 ills. Phila.: Lea & Febiger, 1947. Price, \$4.50.

ALTHOUGH the book is offered as a primer for beginners, the number of physicians who would fail to profit from its study is small indeed. Its emphasis has successfully been "placed upon those cardiac problems which are likely to be of greatest importance in medical practice."

Annual Review of Microbiology. Vol. I. Edited by CHARLES E. CLIFTON, SIDNEY RAFFEL, and H. ALBERT BARKER. Pp. 404. Stanford, Calif.: Annual Reviews, 1947. Price, \$6.00.

IMPORTANT developments in the rapidly growing field of microbiology are considered in the review articles of this collection. The topics include rickettsiae, respiratory viruses, chemotherapeutic agents, immunoelectrochemistry, variation in plant fungi and viruses, growth factors for protozoa, bacterial metabolism, and nitrogen metabolism. All subjects are reviewed by individuals who have done research work in the field concerned. The phases of any given subject that are considered are at times limited, but are always informative. (I. Z.)

NEW EDITIONS

Mind and Memory Training. By ERNEST E. WOOD, former Principal of the D. G. Sind National College, Hyderabad, Sind. 2nd Ed. Pp. 188. London and New York: Pitman Publishing, 1945. Price, \$2.50.

THIS book effectively exhibits the author's knowledge of the history of memory training, including excerpts from the works of John Willis (pub. 1618) and those of "a certain

Major Beniowski," with a special chapter on "Memory-men of India." The few items of practical value are scattered somewhat thinly through this mass of material, and the book has little to offer the psychologist or psychiatrist. (E. B.)

Poisons, Their Isolation and Identification.

By FRANK BAMFORD, B.Sc., late Director of the Medico-Legal Laboratory, Cairo. Revised by C. P. STEWART, M.Sc., Ph.D., Univ. of Edinburgh. 2nd Ed. Pp. 304; 23 ills. Phila.: Blakiston, 1947. Price, \$5.00.

Handbook of Diagnosis and Treatment of Venereal Diseases. By A. E. W. McLACHLAN, M.B., Ch.B. (Edin.), Consultant in Venereal Diseases, City and County of Bristol. 3rd Ed. Pp. 375; 160 ills. Balt., and London: Williams & Wilkins, 1947. Price, \$5.00.

THIS handbook, in 21 chapters, is about equally divided between syphilis and the other venereal diseases. The diagnosis and treatment of all the venereal diseases are adequately covered. The colored plates, especially those showing early generalized syphilis, are excellent. This book should be of great value to the medical student and the general practitioner. (B. H.)

The Foot and Ankle. By PHILLIP LEWIN, M.D., F.A.C.S., Assoc. Prof. of Bone and Joint Surgery, Northwestern Univ. Medical School. 3rd Ed. Pp. 847; 389 ills. Phila.: Lea & Febiger, 1947. Price, \$11.00.

Diseases of the Nose, Throat and Ear. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., late Prof. Univ. of Illinois School of Medicine, and HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assoc. Prof. of Otolaryngology, Northwestern Univ. School of Medicine, assisted by JOHN JACOB BALLENGER, B.S., M.D. 9th Ed. Pp. 993; 597 ills., 16 plates. Phila.: Lea & Febiger, 1947. Price, \$12.50.

Synopsis of Neuropsychiatry. By LOWELL S. SELLING, M.D., Ph.D., Dr.P.H., F.A.C.P., Director, Division of Mental Health, Florida Department of Health. 2nd Ed. Pp. 561. St. Louis: C. V. Mosby, 1947. Price, \$6.50.

THIS book attempts to put all of neurology and psychiatry into 1 volume; the neuroses into 24 pages; psychosomatic medicine into 7; child psychiatry into 30. It is a synopsis for the general practitioner. (E. B.)

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ORIGINAL ARTICLES

STREPTOMYCIN IN THE TREATMENT OF TULAREMIA

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AND

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THE purpose of this report is to summarize the clinical data on 56 cases of tularemia which have been treated with streptomycin in 22 Veterans Administration Hospitals.

Since its first description in 1911,²⁰ tularemia has been the subject of intense and rewarding study by a large number of workers. Its etiology,^{11,29} pathology,^{19,28} epidemiology,^{3,5,13,30} and clinical course^{7,23} have been clearly described and the American literature has become so rich on all phases of the subject up to the introduction of streptomycin that we feel it superfluous to add to this material. The reader is referred to one of the several excellent reviews of the literature.^{7,11,21,23}

Shortly after Schatz, Bugie, and Waksman^{24,25} discovered and described streptomycin and suggested its use in the treatment of diseases caused by a variety of Gram-negative pathogens, Heilman¹² reported its effectiveness against *P. tularensis* both *in vitro* and in rats. From March to July, 1946, the Committee on Chemotherapeutics and other Agents of the National Research Council distributed the antibiotic for clinical trial in a number of different hospitals and, in consequence, published reports of its use in human in-

fection with *P. tularensis* appeared simultaneously from several different workers. Foshay¹⁰ reported in detail his observations on 7 cases and later⁸ extended them to 9 cases. Keefer¹⁷ includes 67 cases in his official report on streptomycin, but goes into no detail concerning them. Nichols and Herrell²² list 15 cases in their general report, Howe *et al.*¹⁵ discuss 7 cases, Abel¹ had 3 cases and Cohen and Lasser⁴ reported 1 case.

Commencing in March, 1946, and for the remainder of the calendar year, the Streptomycin Committee of the Central Office, Veterans Administration, in Washington, D. C., shipped streptomycin by Air Express to its hospitals upon telegraphic notification of appropriate diagnoses. Among the cases thus treated were 56 patients with tularemia. At the request of the Streptomycin Committee and through the extraordinary courtesy and cooperation of the various hospitals and the individual doctors who treated the patients, we have been able to review in detail their complete clinical records for the purpose of this publication.

The clinical classification of human infection with *P. tularensis* into ulceroglandular, oculo-glandular, glandular, and ty-

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phoidal types⁷ has served useful purposes in the study of the clinical course,^{2,7,16,18,26,27} mode of infection,^{3,13} the rôle of insect vectors,^{5,13} and pathology.¹⁹ Blackford and Cassey,² and Pullen and Stuart²³ and others^{7,16,18,26,28} have emphasized the frequency and the importance of pneumonic involvement in all varieties of this infection. In our group of patients the occurrence of pleuropulmonary tularemia, with or without obvious involvement elsewhere, added so much to the gravity and urgency of the clinical problem that it seems desirable to divide the cases into a group of 15 who had notable pneumonic involvement, and a group of 41 without pulmonary infection.

patient's serum. Because of the danger of laboratory infection, few hospitals made serious efforts to recover the organism by culture, and in only 2 cases was the pathogen demonstrated by animal inoculation. In the remainder, the diagnosis in the ulceroglandular cases was suggested by the clinical features of the infection (exposure to possible vectors, primary ulcer, regional lymphadenopathy, and others) and in every case it was confirmed by the presence of specific agglutinins, with rising titer, in the patient's serum. Proof of pneumonic involvement depended upon positive physical findings and serial roentgenograms associated with the presence of specific agglutinins.

TABLE 1.—SUMMARY OF CLINICAL DATA IN 41 CASES OF ULCEROGLANDULAR TULAREMIA TREATED WITH STREPTOMYCIN

Case No.	Day of illness drug started	Total dose (gm.)	No. of treatment days	Average maximum temperature before treatment	After beginning treatment			Condition of lymph nodes at discharge
					Days to clinical improvement	Days of fever	No. of days to discharge	
1	3	6.0	6	100.0	1	4	6	Regressing
2	4	8.4	7	100.0	1	2	17	Normal
3	4	7.0	6	104.0	1	5	8	Normal
4	5	8.0	8	98.8	?	?	15	Normal
5	7	13.2	8	102.0	1	5	17	Normal
6	9	8.0	8	98.4	?	?	27	Normal
7	9	8.0	6	101.0	1	1	14	Normal
8	10	8.8	11	103.0	1	2	13	Normal
9	10	6.0	7	100.4	1	2	8	Regressing
10	12	9.6	8	101.4	1	2	36	Regressing
11	13	4.0	5	102.8	1	2	12	Enlarged
12	13	7.0	4	100.0	4	6	23	Enlarged
13	15	8.0	8	100.8	2	4	53	Draining
14	15	9.1	12	99.4	5	?	14	Regressing
15	15	7.2	6	99.2	?	7	39	Draining
16	16	8.0	6	98.8	?	?	9	Regressing
17	16	9.6	8	98.8	4	4	25	Regressing
18	17	7.0	7	99.2	3?	3	11	Regressing
19	17	8.0	6	?	?	?	15	
20	18	11.5	8	102.1	1	4	18	
21	20	8.0	6	99.5	4	4	14	Regressing
22	21	8.0	8	99.0	?	4	12	Regressing
23	21	12.0	8	100.4	3	4	39	Draining
24	22	4.0	6	99.0	?	?	7	Normal
25	22	11.6	10	101.4	3	8	11	Regressing
26	23	9.0	9	99.8	3	3	36	Regressing
27	26	8.4	7	102.0	2	6	13	Regressing
28	26	20.0	17	99.8	?	6	46	Draining
29	26	10.8	9	99.8	1	2	23	Unchanged
30	29	7.2	6	98.0	?	?	26	Regressing
31	29	8.4	7	99.9	?	?	7	Regressing
32	29	7.0	6	102.2	?	10	26	Regressing
33	30	6.0	6	99.4	?	1	20	Unchanged
34	30	9.6	8	98.4	?	?	9	Regressing
35	32	8.4		100.6	?	?	89	Regressing
36	32	1.92	6	101.6	5	6	49	Draining
37	42	9.6	8	99.2	11	16	51	Draining
38	42	17.6	13	99.0	2	2	41	Draining
39	48	9.6	8	100.0	2	2	8	
40	..	18.6	13	98.4	3	3	71	Regressing
41	90	7.0	7					

Proof of Diagnosis. Absolute proof of etiology in this infection depends upon the isolation of *P. tularensis* from the tissues of the patient, or the presence of specific agglutinins, with a rising titer, in the

Ulceroglandular Tularemia. Forty-one patients with ulceroglandular tularemia were treated with streptomycin. The summary of the clinical data is contained in Table 1.

From the clinical data at our disposal, it is obvious that the criteria for discharge from the several hospitals varied with the individual hospital and with the individual patient. Furthermore, from the clinical records it is impossible to determine the duration of follow-up studies. In general it seems clear that the patients were afebrile for an appreciable period of time, were ambulatory, and were gaining weight, before they were discharged.

completely disappeared at the time of discharge, and in 8 patients there was notable regression. In 2 patients there had been definite enlargement of the nodes, and in 2 patients with discharging buboes drainage was still present at the time of dismissal from the hospital.

In 13 patients, treatment was begun after the 24th day of their illness. In several of these cases the infection was a low-grade chronic process associated with

TABLE 2.—TIME RELATIONSHIP OF STREPTOMYCIN TREATMENT TO SUBSEQUENT COURSE IN ULCEROGLANDULAR TULAREMIA

Days of illness preceding treatment	No. of patients	After beginning treatment		
		Days to clinical improvement	Days of fever	No. of days to discharge
3-12	10	1.00	3.00	20.1
13-24	16	3.00	4.35	21.06
24+	15	3.83	5.32	30.7

In Table 2 the patients are divided into groups on the basis of the duration of illness before treatment was instituted.

In 10 patients, treatment was begun between the 3rd and 12th day of illness. In several of these cases treatment was instituted before serum agglutinins were demonstrated, but in each instance the history, clinical course, and the physical findings were sufficiently suggestive to warrant treatment. In every case the agglutinins appeared subsequently. Each of these 10 patients showed evidence of clinical improvement within 24 hours. They became afebrile within an average of 3 days, and were discharged from the hospital in an average of 20.1 days after the treatment was instituted. In 7 patients, lymphadenopathy had completely disappeared, while in 3 patients there was notable regression of the lymphadenopathy by the time of discharge.

In 16 patients, treatment was instituted between the 13th and 24th day of illness. The average number of days which elapsed before notable clinical improvement was 3. The patients became afebrile, on an average of 4.3 days, and were discharged from the hospital on an average of 21.1 days after treatment was instituted. In 1 patient the lymphadenopathy had

discharging buboes. Clinical improvement in this group was not as prompt or as impressive as when the infection was treated early. For the 7 patients in whom the time could be determined, the average number of days from the institution of treatment to clinical improvement was 3.8; of the 13 patients 10 exhibited fever. The average number of days required for the disappearance of fever was 5.3. The patients in this group were discharged from the hospital on an average of 30.7 days after treatment was begun. In 7 cases there was notable regression, and in 2 patients there was no change in the lymphadenopathy. Four patients had discharging buboes at the time of their dismissal from the hospital.

Pleuropulmonary Tularemia. Fifteen of the group of 56 patients had frank pleuropulmonary involvement. All were treated with streptomycin. Data regarding these cases are summarized in Table 3.

Table 4 indicates the duration of illness before treatment was instituted in patients with pleuropulmonary involvement, the number of days before improvement was noted, and the duration of fever and of hospitalization after the institution of treatment.

In 4 patients treatment was begun

between the 1st and the 12th day of illness. The average number of days until notable clinical improvement occurred was 1.7. The patients became afebrile, on an average, in 3.7 days and were discharged from the hospital, on an average, in 24 days after the beginning of treatment.

sions as well. The remaining 10 were examples of tularemic pulmonary infection in the absence of ulceroglandular lesions and, therefore, constituted difficult diagnostic problems. The importance of correct etiologic diagnosis in such cases is emphasized by the fact that no deaths occurred in our

TABLE 3.—SUMMARY OF CLINICAL DATA IN 15 CASES OF PLEUROPULMONARY TULAREMIA TREATED WITH STREPTOMYCIN

Case No.	Day of illness drug started	Total dose (gm.)	No. of treatment days	Average maximum temperature before treatment	After beginning treatment			Remarks
					Days to clinical improvement	Days of fever	No. of days to discharge	
42 . .	9	5.1	8	104.3	2	6	16	
43 . .	11	6.7	8	103.4	1	2	24	
44 . .	11	8.4	5	100.5	3	3	33	Skin rash attributed to drug
45 . .	12	14.0	7	103.0	1	4	23	
46 . .	14	14.4	7	103.0	1	3	31	
47 . .	14	10.8	9	103.0	1	5	14	
48 . .	15	8.0	5	103.0	1	11	45	
49 . .	17	7.2	6	103.4	1	2	31	
50 . .		6.0	15	103.6	1	15	48	Sixth day of treatment pleural effusion; 12th day thrombophlebitis.
51 . . .	23	21.6	9	103.5	1	7	34	Developed pleural effusion. At discharge Roentgen ray interpretation of residual atelectasis. Condition good at discharge.
52 . . .	24	21.6	18	102.6	3	4	20	
53 . . .	25	7.0	7	102.0	3	14	26	Antiserum prior to streptomycin; 8 days later serum sickness. On streptomycin developed a back abscess requiring drainage.
54 . . .	28	6.4	8	101.4	1	1	67	
55 . . .	34	13.0	13	99.2	?	4	20	
56 . . .	71	7.0	7	100.5	1	3	9	

TABLE 4.—TIME RELATIONSHIP OF STREPTOMYCIN TREATMENT TO SUBSEQUENT COURSE IN PLEUROPULMONARY TULAREMIA

Days of illness preceding treatment	No. of patients	After beginning treatment		
		Days to clinical improvement	Days of fever	No. of days to discharge
0-12	4	1.7	3.7	24.0
12-24	7	1.3	6.7	31.8
24-71	4	1.7	5.5	30.5

In 7 patients treatment was begun between the 12th and the 24th day of illness. The average number of days until notable clinical improvement took place was 1.3. They became afebrile in 6.7 days, and were discharged from the hospital in 31.8 days after the beginning of treatment.

In 4 patients treatment was begun after the 24th day of illness. The average number of days until notable clinical improvement occurred was 1.7. They became afebrile in 5.5 days, and were discharged from the hospital in 30.5 days after treatment was begun.

Five of the patients with pleuropulmonary involvement had ulceroglandular le-

group of 15 cases exhibiting this manifestation of the disease.

Mortality. Mortality figures in a series as small as ours are not statistically valid,⁷ nevertheless it is certainly noteworthy that in a group of 56 patients with tularemia there was only 1 death, and in this case necropsy indicated that tularemia was not primarily responsible. An abstract of this case follows:

Case Reports. CASE No. 41. A 51-year old trapper was admitted to the hospital 6 weeks after developing an ulcer on the left index finger followed by left axillary adenopathy, which had required drainage. On admission there was pain in the right upper

quadrant, an enlarged liver, and jaundice. Tularemia agglutinations were found to be positive in a dilution of 1:320 rising to 1:640. He was therefore started on 1 gm. of streptomycin daily with prompt remission of the fever. His course was steadily downhill and he died on the 6th day of therapy. At autopsy a carcinoma of the pancreas was found with metastases to the liver, spleen, and peritoneum.

Over a fourth of our cases with tularemia had pleuropulmonary involvement. After carefully reviewing the literature in 1941, Blackford and Cassey² concluded that the mortality from the pleuropulmonary form of tularemia is approximately 30%. Every one of our 15 cases with this form of the disease recovered.

Suppurative Lymphadenitis. An analysis of the records of the 56 patients reveals that in 11 cases suppurative lymphadenitis occurred. In 1 case, spontaneous drainage occurred before treatment was instituted; in 10 it became manifest during or after the completion of streptomycin treatment. In each instance, the dosage of streptomycin and the duration of its administration were adequate to produce marked improvement in all of the other manifestations of the disease.

Two of these patients with suppurative lymphadenitis were of special interest because they received 1 gm. of streptomycin daily over a period of several days, but later developed exacerbations of their disease requiring additional therapy. Brief summaries are presented:

CASE No. 40. A 25 year old man was admitted to the hospital with a firm, tender mass in the left epitrochlear area and another in the left axilla. Streptomycin therapy was begun on the 19th day of illness and continued at the rate of 1 gm. daily for 9 days. The epitrochlear node progressed to suppuration and was aspirated while the axillary node regressed very slowly. Two days after streptomycin was discontinued, there was enlargement and increased tenderness of both involved nodes. Ten days after the first course was discontinued, a second course was begun in the same dosage and continued for 9 days. The induration surrounding the nodes again regressed but the nodes themselves progressed to suppuration and both

required drainage 6 days after the second course of the drug was completed.

CASE No. 38. A 44 year old man was admitted with left inguinal adenopathy, one node being fluctuant at the time of admission. Streptomycin was begun on the 42nd day of illness at the rate of 1 gm. per day, and there was prompt remission of his local signs and symptoms. Nine days after completion of the first course of therapy tenderness, swelling, and induration again became apparent, with one node becoming fluctuant. On the 18th day after completion of the first course, a second course was begun at the rate of 1 gm. daily for 7 days. The fluctuant nodes progressed to spontaneous rupture, while there was prompt regression of the remainder of the nodes.

Our experience indicates that the bubo is the most refractory of all tularemia lesions to streptomycin treatment. Slow resolution of the primary ulcer and of pneumonia and pleural reactions have been noted and attributed to the granulomatous nature of the infection. However, the actual progression of lesions of the lymph nodes with liquefaction and discharge while the patient is under streptomycin treatment, or after recovery from systemic manifestations of infection and cessation of treatment, is unique. The explanation of this failure probably resides in the granulomatous nature of the tularemia inflammatory process, the inability of the body fluids to deliver the streptomycin in adequate concentration to the interior of the inflamed lymph node, and the necrosis which may have taken place before the institution of specific therapy. Foshay³ has suggested that a secondary infection of the lymph node is the responsible factor.

Toxic Reactions. Only 3 patients developed skin rashes attributable to streptomycin. Case No. 15 developed urticaria on the 4th day of streptomycin therapy which did not necessitate discontinuing the drug. Case No. 23 developed a slightly raised erythematous rash across the shoulders on the 2nd day of therapy. The drug was continued for an additional 7 days during which time the rash was treated locally and subsided promptly. Case No. 44 developed a pruritic rash on

the trunk and extremities on the 3rd day of streptomycin therapy. Treatment was continued for an additional 2 days and then discontinued because of general improvement. The rash lasted in this patient for a total of 5 days and then cleared without sequelæ.

Immediate Response to Treatment. In those patients whose illness pursued a stormy course there was invariably prompt and dramatic clinical improvement shortly after streptomycin was begun. The temperature usually became normal promptly. Commonly, after the beginning of streptomycin therapy, the induration and tenderness about the involved lymph nodes disappeared, whether the node itself was fluctuant or not. In most instances the patient promptly developed a feeling of well being which was reflected in disappearance of "toxicity," improvement of the appetite, and gain in weight.

Dosage of Streptomycin and Duration of Treatment. The total dosage used in the 56 cases varied from 1.9 gm. to 20 gm., averaging 8.1 gm. There was no difference in the dosage used in the ulceroglandular and the pleuropulmonary cases.

The duration of treatment varied from 4 to 18 days, averaging 9.1 days. The pleuropulmonary cases were treated an average of 2 days longer than the ulceroglandular cases.

No correlation between the duration of treatment and the completeness of recovery can be shown in our study, partly because treatment was continued for much longer periods in those cases in which fluctuant lymph nodes were present.

Brief summaries of 2 cases in which streptomycin was administered for short periods of time and the patients suffered relapses are presented:

CASE No. 16. A 21 year old trapper experienced the onset of chills, fever, and headache with lymphadenopathy in the right epitrochlear and axillary groups, and a characteristic skin lesion on the right index finger 6 days after his last known exposure. On the 6th day of his illness he was admitted to a private hospital and started on streptomycin, receiving 0.125 gm. every 3 hours.

After he had received 16 doses (2 gm.) he was free of symptoms. He left the hospital and resumed his normal activity. Three days later chills, fever, headache, and malaise recurred. He was admitted to the same hospital and started on the same dosage of streptomycin. After he had received a second course of 16 doses (2 gm.) he again experienced marked symptomatic improvement and was discharged to return to work. Four days later he again experienced chills, fever, headache, and axillary tenderness. At this point he was admitted to a Veterans Administration Hospital. He was given 1.25 gm. of streptomycin every 24 hours for 6 days (7.5 gm.) with complete and permanent recovery.

CASE No. 19. A 34 year old trapper experienced the onset of headache, chills, fever, and axillary tenderness 4 days after his last known exposure. He had a questionable skin lesion on the right hand. On the 6th day of his illness he was given streptomycin in a private hospital. He received 0.125 gm. of streptomycin every 3 hours. After he had received 12 doses (1.5 gm.) his symptoms had improved so markedly that he left the hospital and returned to work. Three days later he developed chills, fever, axillary tenderness, and malaise, and was admitted to a Veterans Administration Hospital. He was found to have tender nodes in the right axilla and a white blood count of 11,600. Agglutinins against *P. tularensis* were present in a dilution of 1:1280. He was given 1.25 gm. of streptomycin daily for 6 days and promptly recovered.

That the duration of treatment is perhaps as important as the total dose of streptomycin is suggested by comparing the result in Case No. 36 with that in Cases No. 16 and No. 19.

CASE No. 36. A 51 year old tailor experienced the onset of fever, chilly sensations, and tender swelling in the left groin 5 days prior to his admission. Examination revealed temperature of 103.8, tender lymphadenopathy in the left groin, a white blood count of 13,300, serum agglutinins against *P. tularensis* in dilution of 1:20, with subsequent rise to 1:4000 on the 26th day of his illness. On the 32d day of illness he was started on streptomycin 0.04 gm. every 3 hours continued over a period of 6 days (1.92 gm.). There was marked clinical improvement and he became afebrile on the

5th day of his treatment; lymphadenopathy disappeared and recovery was complete.

Four of our cases of pleuropulmonary tularemia received only 0.4 to 0.8 gm. of streptomycin every 24 hours for periods of from 5 to 7 days. Three of these patients were gravely ill at the time treatment was begun. All 4 experienced prompt improvement and proceeded to complete recovery.

Summary. The records of 56 patients with tularemia treated with streptomycin in Veterans Administration Hospitals have been reviewed. Of this group, 15 cases were examples of pleuropulmonary tularemia. The pleuropulmonary infection occurred as a complication of the ulceroglandular form of the disease in only 5 cases. In the remaining 10, no primary site of infection other than the lung or the pleura could be determined.

The only death which occurred in the

series was attributed to carcinoma of the pancreas.

Streptomycin, when administered after the 12th day of illness, appears to have little effect upon the course of suppurative lymphadenopathy. Liquefaction and spontaneous drainage of lymph nodes may occur under such circumstances, even though there is striking improvement in the other manifestations of the disease.

Only 3 patients demonstrated sensitivity to streptomycin. In none of these cases was it necessary to discontinue the drug.

Streptomycin was highly effective in the treatment of every case of tularemia in this series. In the acutely ill patient pursuing a stormy course, its effect was most dramatic.

The dosage and duration of streptomycin administration varied considerably in the cases reviewed.

We wish to express our appreciation for the courtesy and cooperation of the Managers and Medical Staff of the following Veterans Administration Hospitals for permission to include their cases in this review: Whipple, Arizona; Fayetteville, Arkansas; Fargo, North Dakota; Chamblee, Georgia; Hines, Illinois; Marion, Illinois; Fort Benjamin Harrison, Indiana; Topeka, Kansas; Wadsworth, Kansas; Wichita, Kansas; Minneapolis, Minnesota; Jefferson Barracks, Missouri; Dayton, Ohio; Muskogee, Oklahoma; Memphis, Tennessee; Mountain Home, Tennessee; McKinney, Texas; Huntington, West Virginia; Wood, Wisconsin; Cheyenne, Wyoming; and Sheridan, Wyoming. Dr. Arthur M. Walker assisted us in gathering clinical material for study, and Dr. Hugh J. Morgan gave us much valuable advice in constructing this report.

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PROCAINE PENICILLIN G IN OIL

I. PLASMA CONCENTRATIONS; PRELIMINARY OBSERVATIONS ON ITS USE IN PNEUMONIA

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PROLONGATION of the effectiveness of a given dose of penicillin would be most desirable. Attempts to prolong the action of the drug have endeavored either to hinder the drug from reaching the circulation by slowing the absorption from the site of its injection, or by retarding the rate of its elimination by the renal tubules.

The use of penicillin suspended in peanut oil and beeswax has been reasonably successful in prolonging therapeutically effective concentrations following single injections of the drug. A quantity of water-soluble salt of penicillin suspended in oil and wax constitutes a reservoir from which penicillin is slowly given up to the body fluids. The beeswax is responsible on the one hand for the prolongation of blood concentrations of penicillin following its injection, and, on the other, the cause of most of the disadvantages attendant upon its use. Beeswax gives rise to allergic manifestations, sterile abscesses, and pain following its injection, and, although severe reactions are few, the occurrence of pain and induration at the site of injection is frequent enough to prejudice many physicians against its use.

During the early development of penicillin, little interest was manifested in

many of the salts of penicillin by reason of their relative insolubility in water and attention was focused almost entirely on those that were water-soluble. The suspension of a water-soluble salt of penicillin in a *milieu* of oil and wax has been shown to effectively slow the release of penicillin from the site of its injection into the circulation, and the use of large particle sized of penicillin crystals¹ has further retarded the rate at which penicillin is dissipated from the oil and wax reservoir. The possibility of suspending a penicillin salt, relatively insoluble in water, in an oil phase and thus obtain an even slower release of penicillin from the injection site, has one recently been investigated.⁷ Procaine-penicillin is the first of these salts to be submitted for clinical evaluation and it is the purpose of this paper to report preliminary observations on the use of procaine penicillin G suspended in oil.*

MATERIAL USED. Procaine and penicillin G are combined in equimolecular quantities to form a crystalline salt relatively insoluble in water (less than 0.7% at 28° C.). The particle size of the crystals of this salt is controlled so that at least 50% of the crystals are more than 50 microns in length. The theoretical

* The authors wish to thank Dr. N. P. Sullivan, of Eli Lilly and Company, for kindly supplying procaine penicillin G in oil (Duracillin, Lot No. S169-P45724 and Lot No. 8044-P45573) for this study and for making available preliminary information pertaining to this preparation.

potency of this preparation should be 1040 units per mg., but potency by test is 940 units per mg. Not less than 90 % of the penicillin in this preparation is penicillin G and approximately 41.5 % of the weight of this salt of penicillin is procaine. About 7000 units of this salt of penicillin can be dissolved in 1 cc. of water.

Procaine penicillin crystals, such as described above, were suspended in both cottonseed and sesame oils so that each cc. of material contained 300,000 units of penicillin and 125 mg. of procaine. Although both of these preparations were employed in this investigation, the latter proved to be superior by reason of greater stability and fluidity. Whereas the suspension in cottonseed oil must be injected through a No. 18 gauge needle, the sesame oil suspension can be injected through a No. 21 gauge needle. Since the penicillin settles out of either suspension on standing vigorous shaking is required to restore the homogeneity of the preparation. Slight warming facilitates injection of the material through a No. 21 needle.

METHODS EMPLOYED. Blood specimens for penicillin assays were drawn, with sterile technique, into citrate solution, transferred to graduated centrifuge tubes, centrifuged and the plasma pipetted off. Plasma samples were immediately refrigerated and transported to the laboratory for assay. Penicillin assays were done by a modified Rammelkamp serial dilution method, using a Group A hemolytic streptococcus as the test organism. Correction for the dilution factor introduced by the use of citrate solution was made in all instances.

PATIENTS STUDIED. Nine ambulatory patients, free of manifest hepatic, cardiac, and renal disease, who were afebrile and partaking freely of fluids and food, were chosen as control patients for this study.* Each patient received 1 cc. (300,000 units) of procaine penicillin suspended in oil as an intramuscular injection into the left

buttock. Massage of the injection site was avoided. Thereafter, at 1, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours respectively, blood specimens were drawn for penicillin assay. This schedule of sampling was adopted in order that bleedings might be done at 9 A.M., 3 P.M., and 9 P.M., times which interfered least with hospital routine.

Eleven consecutive patients admitted to the hospital with lobar pneumonia, as determined by history, physical examination, Roentgen ray examination and laboratory findings, were treated with 1 cc. (300,000 units) of procaine penicillin administered as a single intramuscular injection into the left buttock. No additional therapy in the form of sulfonamides or penicillin was given, until such therapy was indicated by an adverse clinical course. The blood sampling schedule on these patients conformed to that outlined above to the extent that specimens were drawn at 9 A.M., 3 P.M., and 9 P.M. Since, however, patients received the injection of procaine penicillin immediately upon entrance to the hospital, the hours at which penicillin assays were done with reference to this injection do not conform with those of the control group. This program resulted in obtaining information regarding plasma concentrations at intervals not studied in the control group.

The next 12 patients admitted with the diagnosis of pneumonia, were given a single intramuscular injection of 2 cc. (600,000 units) of procaine penicillin into the left buttock without massage of the site. No additional therapy was given until the necessity of it was indicated by the patient's clinical course.

Results. Table 1 presents the blood concentrations of penicillin following the administration of 300,000 units of procaine penicillin to 9 control patients. With the exception of patient J. B., who showed assayable quantities for 30 hours, the penicillin concentrations fell below 0.039 unit per cc. of plasma some time between 12

* Clinical facilities were given us for this study by the following Chiefs of Service: Drs. Frieda Baumann, R. S. Boles, T. M. Durant, H. L. Goldburgh, D. W. Kramer, D. N. Kremer, W. G. Leaman, Jr., T. G. Schnabel, and C. M. Thompson.

and 24 hours after the injection. One hour after the injection, the penicillin plasma concentrations ranged from 0.337 to 2.73 and thereafter declined rather regularly to values lower than could be detected by the method of assay used.

In Table 2 are shown the plasma concentrations that resulted from the injection of 300,000 units of procaine penicillin suspended in oil into patients suffering from pneumonia. Penicillin was detectable for less than 16 hours, less than

TABLE I.

Plasma Concentrations Following 300,000 Units Procaine Penicillin in Oil CONTROL PATIENTS*

Hours After Injection**	LW 27/M***	CW 62/M	JB 55/M	LE 49/M	JM 18/M	WP 40/M	BM 24/M	CT 31/M	RW 15/M	Average
1	2.73	1.97	0.337	2.05	1.36	0.908	0.908	1.81	1.81	1.54
6	0.678	1.39	0.690	1.33	0.452	0.451	0.908	0.228	0.453	0.729
12	0.043	0.043	0.341	o	0.113	0.042	0.084	0.057	0.042	0.0873

24	o	o	0.085	o	o	o	o	o	o	o
30	o	o	0.042	o	o	o	o	o	o	o
36	o	o	o	o	o	o	o	o	o	o
48	o	o	o	o	o	o	o	o	o	o
54	o	o	o	o	o	o	o	o	o	o
60	o	o	o	o	o	o	o	o	o	o
72	o	o	o	o	o	o	o	o	o	o

*All of these patients were ambulatory.

**Injection was made routinely into left buttock without massage of the site.

***Age/Sex.

****Concentrations less than 0.039 units/cc. have been regarded as zero.

TABLE II.

Plasma Concentration Following 300,000 Units Procaine Penicillin in Oil PNEUMONIA PATIENTS

Hours	MK* 33/F**	Hours	EF 39/F	Hours	LH 22/F	Hours	LR 19/M	Hours	WL 37/M	Hours	AC 43/M	Hours	FW 35/M	Hours	JH 69/M	Hours	TM 77/F	Hours	U 69/M
1	272	1	0.34	9	0.338	16	o	11	0.680	20	0.453	12	0.683	13	0.340	10	0.34	4	1.82
7	0.342	6	0.244	21	0.043	22	o	17	0.340	26	0.228	18	0.225	19	0.227	16	0.341	16	0.113

19	o	18	0.113	27	o	28	o	23	0.227	32	0.171	24	0.227	24	0.170	21	0.34	22	0.058
25	o	24	0.113	33	o	40	o	35	0.113	44	0.057	36	0.056	36	o	34	0.17	28	0.057
31	o	30	0.057	45	o	46	o	41	0.056	50	o	42	o	43	o	40	0.114	40	o
43	o	42	o	51	o	52	o	47	o	56	o	57	o	49	o	46	0.134	46	o
49	o	48	o	57	o	64	o	59	o	68	o	60	o	61	o	58	0.057	52	o
54	o	54	o	69	o	70	o	65	o	74	o	66	o	67	o	64	0.113	64	o
67	o	66	o	76	o	76	o	70	o			72	o	73	o	70	0.113	70	o
73	o	72	o																

* The patient was later shown to have tuberculosis.

** Age Sex.

*** Concentrations less than 0.039 units/cc. have been regarded as zero.

19 hours, and slightly more than 21 hours showed penicillin concentrations above 0.039 unit per cc. for periods varying respectively. The remaining 7 patients from 24 to 70 hours.

PNEUMONIA PATIENTS

Treated with Single Intramuscular Injection of 300,000 Units Procaine Penicillin in Oil

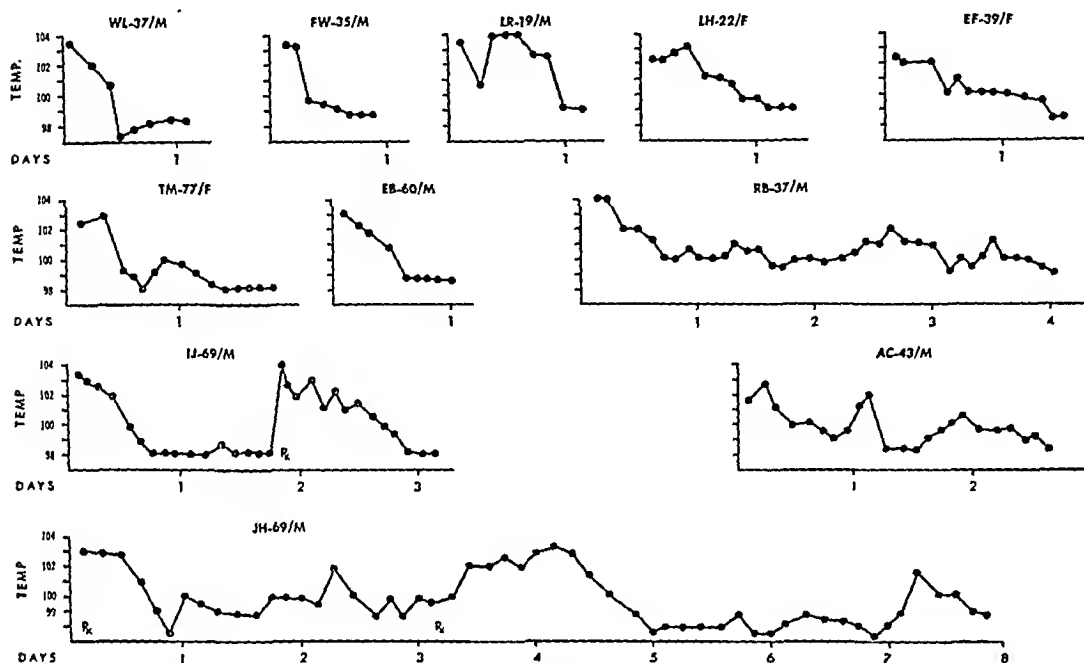


CHART 1

PNEUMONIA PATIENTS

Treated with Single Intramuscular Injection of 600,000 Units Procaine Penicillin in Oil

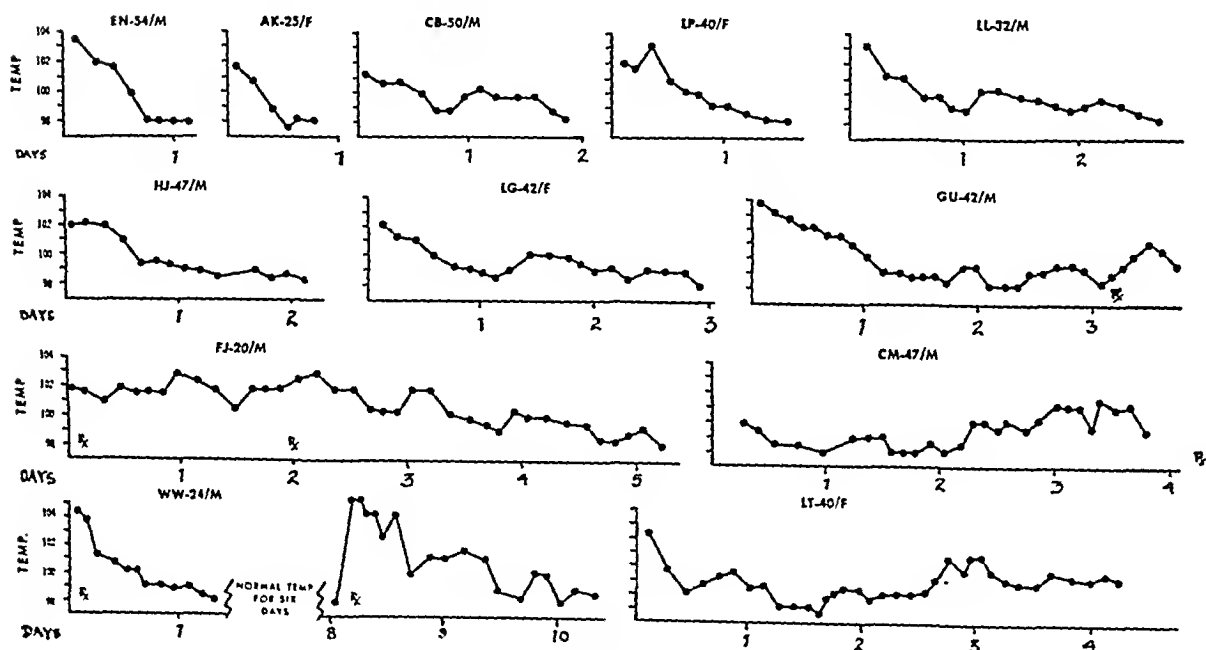


CHART 2

Temperature is one objective criterion by which to judge the response of pneumonia to treatment. In Chart 1 are presented the temperature records of pneumonia patients treated with a single injection of 300,000 units of procaine penicillin suspended in oil. All of these patients responded with a fall in temperature and commensurate clinical improvement and 8 patients went on to complete recovery without further treatment. One patient, R. B., recovered without additional therapy but the response was unsatisfactory and 2 patients, I. J. and J. H., relapsed and required supplementary penicillin therapy.

Chart 2 shows the temperature curves of 12 patients, each of whom received a single intramuscular injection of 600,000 units of procaine penicillin. Eight patients responded satisfactorily without additional therapy. A single patient did not respond to treatment but the fever fell by lysis after secondary procaine penicillin treatment (F. J.). Two patients responded but had return of fever which occasioned second injections of procaine penicillin (C. M. and L. T.), and 1 patient (W. W.) frankly relapsed after 8 days but responded promptly to routine penicillin therapy, 37,500 units intramuscularly every 3 hours.

Discussion. Procaine penicillin in oil, administered intramuscularly into the buttocks of 9 ambulatory and afebrile subjects, resulted in penicillin plasma concentrations above 0.039 unit per cc. for longer than 12 hours in all but 1 patient (L. E.). This patient and one who showed assayable concentrations for 30 hours (J. B.) represent the widest variations in this group. In 10 pneumonia patients, 1 of whom was later shown to have tuberculosis as well, plasma penicillin concentrations above 0.039 unit per cc. were observed for periods varying between 7 to 70 hours. It is suggested that the patients in the control group were ambulatory and well-hydrated and that this circumstance

avored the more rapid elimination of penicillin from the reservoir at the site of injection. On the other hand, the acute illness of the pneumonia patients undoubtedly contributed to the prolongation of detectable penicillin levels in the blood. Variability in both the duration and the height of penicillin concentrations following the injections of penicillin in beeswax and peanut oil has been previously observed and related to activity.³ The long duration of significant concentrations in the case of patient T. M. (age 77 years) is almost certainly related to renal impairment due to age.⁶

Although the group of patients here reported is small, it is of interest to observe that the duration of levels of penicillin above 0.039 unit per cc. for longer than 12 hours in the control group compares favorably with results that have been obtained with penicillin suspended in beeswax and oil at the same level of dosage. Kirby and his associates³ found that following administration of 300,000 units of penicillin in beeswax and oil they failed to demonstrate penicillin in the plasma beyond 12 hours in 37 of 54 patients (69%). The prolongation of significant levels in the group of pneumonia patients is certainly equal to that reported for penicillin suspended in beeswax and oil.^{4,5}

The duration of penicillin in the blood is not the only consideration, however, and if the prolonging effect of procaine penicillin suspended in oil proves equal to that of penicillin suspended in peanut oil and beeswax, the factor of pain incident to the injections may prove to be the more important. Although severe allergic manifestations and actual abscess formation are relatively uncommon, pain and discomfort are very common following use of the beeswax preparation,¹ particularly when repeated doses are administered.² The freedom from pain at the site of injection and the lack of systemic toxicity in a group of 50 patients has been gratifying. A single patient, having a history of

food allergy, developed urticaria the day following the single injection. It has not been determined whether the procaine in combination with penicillin still exerts its anesthetic action, but this is being investigated.

In this connection it should be observed that the presence of significant amounts of procaine in procaine penicillin, 125 mg. per 300,000 units of penicillin, suggests the possibility of either aggravating a previously existent sensitivity or establishing a procaine sensitivity. Conclusions on this point must await extensive clinical usage of the material.

In this preliminary investigation of the use of procaine penicillin suspended in oil in the treatment of pneumonia, no effort was made to establish a single injection of the material as the routine therapy of pneumonia, but rather to investigate the duration of activity of a single large dose of penicillin by measuring penicillin in the blood down to a level which is accepted as having therapeutic significance with regard to the organisms ordinarily associated with bacterial pneumonia, and also by determining the actual duration of antibacterial effect or suppressive effect upon an acute infection amenable to penicillin therapy, bacterial pneumonia.

Attention has already been called to the penicillin plasma concentrations in Table 2, but it is of interest to correlate these concentrations with the temperature curves in Chart 1. In no instance was there a recrudescence of fever while a level of penicillin above 0.039 unit per cc. was being maintained (patients W. L., F. W., L. R., L. H., E. F., T. M., I. J., J. H. and A. C.). The abrupt rise in temperature of I. J. suggests, therefore, the termination of the suppressive antibacterial action of the previously administered penicillin. Patients A. C. and J. H. show rises of temperature almost immediately after assayable quantities of penicillin disappeared from the blood, but in the first case the patient's immunologic defenses permitted recovery without ad-

ditional therapy, whereas this was required in the second case. Penicillin assays were not done on the group of patients who received 600,000 units of penicillin as a single intramuscular injection, but on the basis of the correlation shown above between disappearance of penicillin from the plasma and recrudescence of fever, the recurrence of temperature (Chart 2) in patients G. U., C. M. and L. T. on the 3rd day after treatment is highly suggestive that the antibacterial effect of penicillin had run its course. On the basis of both penicillin assays in the blood and therapeutic response of bacterial pneumonias to a single injection of 300,000 and 600,000 units of procaine penicillin respectively, it is implied that an average period of therapeutic efficacy is 24 to 48 hours. Investigations with intramuscular injections of procaine penicillin at intervals of 24 and 48 hours are in progress and will be the subject of another communication.

Summary and Conclusions. 1. No local pain or systemic toxicity have been observed in 50 patients to whom procaine penicillin G has been administered.

2. The duration of penicillin plasma concentrations above 0.039 unit per cc. varied from 6 to 30 hours in a group of 9 ambulatory control patients. In a group of 10 pneumonia patients it varied from 7 to 70 hours. The averages in the 2 groups were 12 hours and 33 hours respectively.

3. Eighteen of 23 patients suffering from bacterial pneumonia recovered without complication following a single intramuscular injection of procaine penicillin G in oil. Two patients relapsed under this therapy and 3 failed to respond.

4. On the basis of these preliminary data, it appears that a single injection of 300,000 units of procaine penicillin will, in the average patient, give assayable plasma concentrations of penicillin, or a suppressive antibacterial action, for at least 24 hours.

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MYOCARDIAL CHANGES IN FATAL DIPHTHERIA

A SUMMARY OF OBSERVATIONS IN 221 CASES

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DESPITE the continuous downward trend of the incidence of diphtheria in the United States since the practice of immunization became widespread, the disease has not been conquered. Edsall⁶ pointed out that the tremendously decreased carrier rate in artificially immunized communities has been associated with a rising incidence of susceptibility as indicated by the Schick test. Furthermore, the reduced

the peak appears to have been passed in many of these countries, even the most recent figures are considerably above the prewar annual median incidence. Liebow and Bumstead¹³ have traced localized outbreaks in U. S. Army General Hospitals to the introduction into the wards of unrecognized cutaneous diphtheria. A recent report¹⁴ noted a significantly greater number of cases of diphtheria during 1946

TABLE 1
A. Cases of Diphtheria Reported in European Countries*

Country	Pre-war annual median	Number of cases reported annually		
		1943	1944	1945
Belgium	2,089	16,072	6,295	5,808
France	19,389	46,539	40,430	37,262
Germany	78,452	241,609	207,392	..*
Netherlands	3,967	56,825	60,226	78,098
Norway	968	22,787	13,547	7,466
Sweden	1,484	2,496	6,040	4,615

B. Annual Incidence of Diphtheria Among U. S. Troops (Per 100,000)†

	1942‡	1943	1944	1945
Total Army	3.76	9.72	21.44	53.81
Troops within the U. S.	2.52	3.54	6.83	15.66
Troops outside U. S.	9.39	30.01	38.20	81.19

(Figures from Medical Statistics Division, S. G. O.)

* Complete data not available. Compiled from figures in References 2 and 3, UNRRA Epidemiological Information Bulletins, Vols. 1 and 2, 1945, 1946, and Public Health Reports Vol. 61, No. 7, 2-15-46.
† All rates shown are preliminary.
‡ The rates shown for the year 1942 are based on sample tabulations of individual medical records, while those for the last 3 years are based on the Weekly Statistical Health Report, which source probably overstates the actual incidence.

exposure to diphtheria bacilli with the concurrent loss of its stimulating effect has contributed to the more rapid waning of artificially induced immunity.⁶ Such circumstances set the stage for a widespread reappearance of the disease should the virulent organisms be introduced into the population. Considering the present incidence of diphtheria in several of the European countries^{20,21} (Table 1, A) the possibility is far from remote. Though

in both New York City and New York State than during similar periods of 1945. The introduction of large numbers of U. S. troops into areas where the endemic diphtheria rate was high resulted in a striking increase of the incidence of that disease among them (Table 1, B). The situation among occupying troops has not changed since the end of the conflict.⁶ Though no studies have been reported, it is highly probable that the number of

carriers among returned military personnel is greater than among the general populace.

In view of these developments and their ominous potentialities it is thought appropriate and timely to report a study of that sequela of diphtheria which is most often lethal, myocarditis. During a more inclusive review of the subject of myocarditis¹⁰ a large number of cases were found to be associated with diphtheria. The present study is based on a review of the autopsy records and slides of 221 fatal cases of diphtheria accumulated at the Army Institute of Pathology. Material from the heart was available for review in 205 of these. The presence or absence of myocardial disease was determined in each case from the few routinely taken sections of the myocardium. In many instances fat stains, Gram stains, or Giemsa stains of involved heart muscle were prepared. For reasons which will become apparent in the text it was also considered important to ascertain the presence or absence of peripheral neuritis. The latter was determined solely from the clinical records because the available material was inadequate for pathologic study. Though there is a disparity in the method of diagnosis, the clinical report of neuritis is regarded as a sensitive and reliable index of its presence since it is a common experience for pathologists to find a paucity of morphologic changes in nerves to explain rather striking symptoms of nerve injury. The number of instances of myocarditis and peripheral neuritis encountered is listed in Table 2.

TABLE 2.—SEQUELÆ ENCOUNTERED IN 205 FATAL CASES OF DIPHTHERIA

	Cases	%
Myocarditis alone	99	48.3
Myocarditis with neuritis*	44	21.5
Neuritis* alone	6	2.9
No sequelæ	56	27.3
Total	205	100.0

* The presence or absence of neuritis was determined solely from the clinical records, whereas the diagnosis of myocarditis was based on the pathologic findings.

Age. The age distribution of the patients of this series is listed in Table 3. Exclusive of those younger than 18, it was found that 51% of the series was made up of individuals of under 25 years of age, a group constituting 43% of the Army, which was the source of the bulk of this material. The greater susceptibility of younger persons to diphtheria has long been recognized. However, Geiger⁹ has commented upon a noticeable shift in incidence from early age groups to those of 30 years and over; an observation easily explained by the conditions discussed in the introductory paragraphs.

TABLE 3.—AGE DISTRIBUTION OF PATIENTS WITH FATAL DIPHTHERIA

Age group	Cases	%
0-9	22	10.8
10-19	31	15.3
20-29	95	46.8
30-39	48	23.6
40 and over	7	3.4
Unknown	18	..
Total	221	100.0

Color. There was no significant difference between diphtheria rates for white and Negro as far as can be determined from the fatal cases studied. Seventeen, (7.2%) of the patients were non-white, a figure comparable to the proportion (approximately 10%) in the whole army.

Sex. The number of women was far too few to permit analysis of possible sex differences.

Clinical Observations. *Duration of Illness.* The reported duration of illness varied from 1 to 182 days and is summarized in Table 4. Three-fourths of the deaths occurred from 6 to 24 days after the onset of diphtheria. The incidence of

TABLE 4.—LENGTH OF ILLNESS IN 221 CASES OF FATAL DIPHTHERIA

Days	Patients	%
0-1	5	2.8
2-5	27	15.2
6-12	59	33.1
13-24	48	27.0
25-35	18	10.1
46-75	18	10.1
Over 75	3	1.7
Unknown	43	..
Total	221	100.0

both myocarditis and neuritis rose progressively with the duration of illness before death, a relation shown graphically in Chart 1. Age had no apparent relation to the development of either sequela. Myocarditis was present in 70% of the patients who died between the 6th and 24th day, the average duration of illness in these individuals being 14 days. Peripheral neuritis, on the other hand, appeared to develop somewhat later, generally between the 13th and 45th days, the average duration of illness before its onset (among patients in whom symptoms of this condition were reported to have appeared before death) being about 20 days.

TABLE 5.—MANIFESTATIONS OF CARDIAC DYSFUNCTION IN 143 FATAL CASES OF DIPHTHERITIC MYOCARDITIS

	Patients	%
Shock*	74	51 4
Cyanosis	56	38 9
Congestive failure†	49	34 0
Tachycardia	47	32 6
Dyspnea	32	22 2
Substernal pain or oppression	16	11 1
Arrhythmia	11	7 6
Orthopnea	4	2 8
None	9	6 2

* Includes hypotension, weak thready pulse, and imperceptible heart action.

† Includes venous distension, pulmonary edema, hydrothorax, and painful, swollen liver.

Cardiac Manifestations. Signs and symptoms (Table 5) indicative of seriously impaired heart function were present in most of the patients studied, but in a large proportion the presence of myocarditis had not been suspected before death. In many instances, however, the brevity of the interval between the cardiac manifestations and death precluded such recognition. Furthermore, in one-third of the patients the local lesion had resolved and the fever had subsided for a varying interval prior to the onset of cardiac dysfunction. In Chart 2 this latent period has been designated as the "deceptive interval of apparent improvement." Electrocardiograms were made on 52 patients (presumably because of the presence of cardiac symptoms) and abnormalities were present in all of them (Table 6).

TABLE 6.—ELECTROCARDIOGRAPHIC ABNORMALITIES IN 52 PATIENTS WITH DIPHTHERITIC MYOCARDITIS

Delayed conduction	19
Other conduction disturbances	14
"Myocardial damage"	18
Extrasystoles	4
Ventricular tachycardia	4
Tachycardia (type unspecified)	2
Abnormality not specified	9

Neuritis. Neuritis, symptoms of which were reported for 50 patients, involved the cranial nerves first and most frequently. The manifestations included difficulty in swallowing, regurgitation of food, nasal voice, interference with phonation, and visual disturbances. Evidence of involvement of the nerves to the extremities as indicated by pain, weakness, absent reflexes, or paresis was observed in 26 patients. In no instance were the nerves to the limbs affected in the absence of cranial nerve damage. Among the patients with neuritis, those dying between the 6th and 29th day of illness had neurologic manifestations largely limited to the cranial nerves. Patients surviving beyond 24 days included most of those with clinical evidence of involvement of the nerves to the arms or legs. Therefore, both from the number of cases and the duration of illness among them, it would seem that cranial nerves are more susceptible than peripheral nerves.

Complications. Pneumonia, usually of the patchy variety, was by far the most frequent complicating illness. It was present in 50% of the patients who died within 5 days of the onset of diphtheria, and in 86% of those who lived longer than 45 days. Altogether pneumonia occurred in 134 of the 221 fatal cases. The pneumonic process was associated with pericarditis in 5 patients and bacteremia in 4; in a single instance it was associated with Ludwig's angina.

Pathologic Alterations In the Heart.
Gross Observations. Although many of the autopsies were done under wartime field conditions by men without special pathologic training, gross cardiac abnormalities were reported in 71% of the cases. Dilatation of the chambers, flaccidity, pallor,

and "streakiness" of the myocardium, noted singly or in combination, were the changes most frequently reported. In a few cases of prolonged illness small focal areas of scarring were observed. Occasionally, small mural thrombi were found in the left ventricle. Relating these gross features with the microscopic findings described below revealed a direct correlation between them; when the latter indicated severe involvement, gross ab-

normalities were almost invariably reported (Table 7).

TABLE 7.—GROSS CARDIAC ABNORMALITY IN RELATION TO ESTIMATED DEGREE OF MYOCARDITIS

Myocarditis	Number of patients	% showing abnormality
Absent	59	50.8
Slight	17	58.8
Moderate	85	84.7
Severe	34	97.1
Total	195	

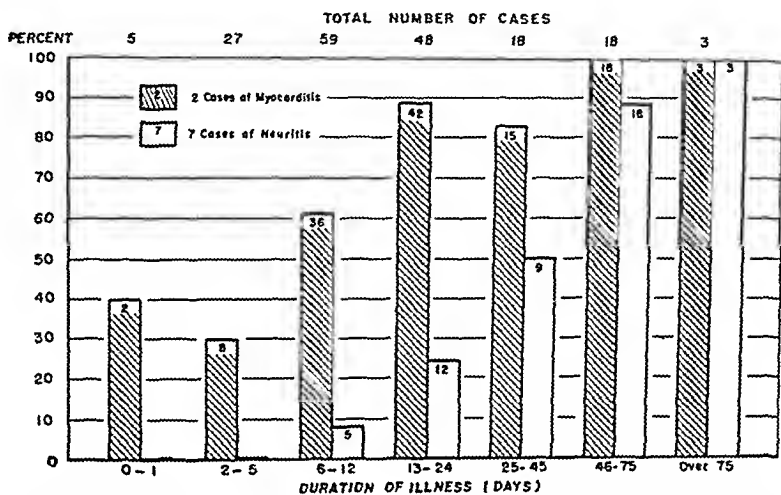


CHART 1.—The relation of myocarditis and peripheral neuritis to the duration of fatal diphtheria.

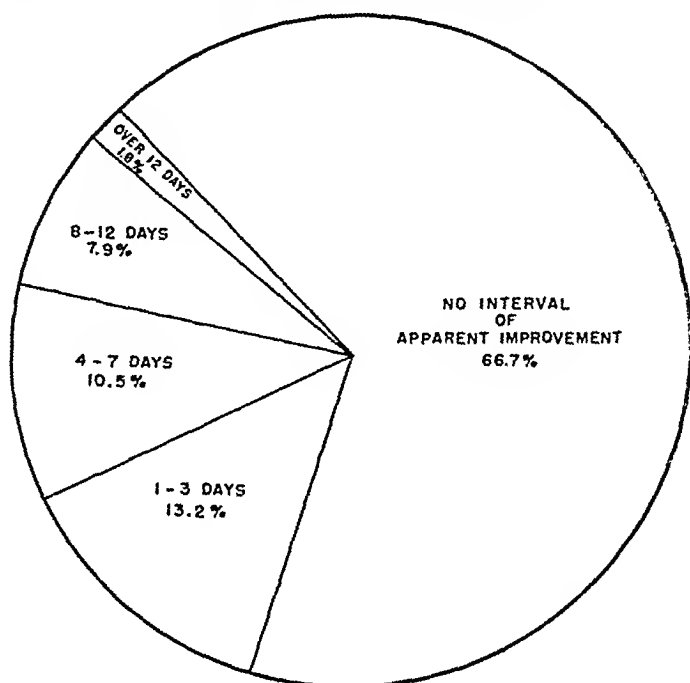


CHART 2.—Duration of deceptive interval of apparent improvement in 221 cases of fatal diphtheria.

Heart Weight. The weight of the heart was found to be increased in some cases in the absence of a history of hypertension, kidney disease, heart disease, heart valvular lesion, or other condition known to be associated with myocardial hypertrophy. Sufficient data were available in 134 cases to utilize the tables of Smith¹⁸ as a criterion of such an increase (Table 8). Increased heart weight was present in more than one-half of the 93 patients with myocarditis. More impressively, 86% of the enlarged hearts were the seat of myocarditis and, as is evident in the table, the severity of that process seemed to bear a direct relation to the degree of cardiac enlargement as well as to its presence.

TABLE 8.—DEGREE OF MYOCARDITIS IN RELATION TO MEAN EXCESS OF HEART WEIGHT OVER NORMAL*

Degree of myocarditis	Number of cases	Mean excess of heart weight (gms.)
None	24	32
Slight	7	52
Moderate	46	84
Severe	17	104

* Heart weight computed in relation to body weight in accordance with tables of H. L. Smith, American Heart Journal, Vol. 4, 1928.

Microscopic Observations. As has been already intimated, the extent of the myocardial changes varied considerably from severe involvement with large and multiple areas of muscle damage to mild changes with only occasional small foci of involvement. In all cases, however, the qualitative changes were identical. Organisms were not demonstrable microscopically in any of the involved hearts. The sequential changes in the myocardial lesion from the onset of diphtheria to the fatal outcome are characteristic, and by studying them one may make a fair estimate of the duration of illness. When death occurs early in the course of the disease, changes are inconspicuous, consisting of mild interstitial edema and cloudy swelling of the muscle fibers. The cells of the interstitium are hyperplastic and plump but not increased in number, and there is no inflammatory cellular infiltrate.

If the disease has gone on for a week,

fairly conspicuous lesions of the cardiac muscle become apparent. Diffusely scattered foci of hyaline and granular degeneration involve segments of the muscle fibers which frequently are attenuated, severely fragmented, or ruptured. A mild, stromal inflammatory response is often observed intrafascicularly adjacent to injured muscle, but the large interfascicular stromal septa are relatively unaffected. The cellular reaction is believed to be in the nature of a reparative response, since it takes place only in the presence of damaged muscle, whereas muscle damage may occur without significantly increased stromal cellularity. The infiltrate consists largely of histiocytic cells, many of which have the characteristics of the so-called "myocyte" of Anitschkow,⁷ indicating that they have arisen *in situ*. A small number of lymphocytes and plasma cells are present; polymorphonuclear leukocytes, eosinophils, mast cells, and others are even more infrequent and seem not to play an essential rôle in the process. The muscle lesion, as has been reported by other observers,³ involves especially the inner portion of the myocardium and the papillary muscles. There is no apparent predilection for any particular one of the heart chambers, nor does the conduction bundle appear to be more or less susceptible than other portions of the musculature.

During the second week, plasma cells and lymphocytes become more numerous although the histiocyte remains the predominant cell type (Fig. 1). Hyaline and granular degeneration is still extensive, with the addition of small foci in which muscle fibers have disappeared, leaving a loose stromal net, moderately infiltrated with macrophages and small round cells. A few macrophages contain brown, granular pigment.

Myolysis, disintegration, or "dropping out" of the degenerated muscle fibers becomes conspicuous during the third week. Grossly, the myocardium appears "streaky," and microscopically the heart

appears "moth-eaten" because of the irregular foci of parenchymal loss. In such foci there is little more than the pre-existent stroma with hyperplastic cells containing an infiltrate of histiocytes, plasma cells, and lymphocytes. Areas of

muscle loss, show marked hyperplasia and abortive regeneration (Fig. 2). If such an area happens to be immediately adjacent to the endocardium, the alterations in that layer may lead to the formation of a mural thrombus.^{5a,22}

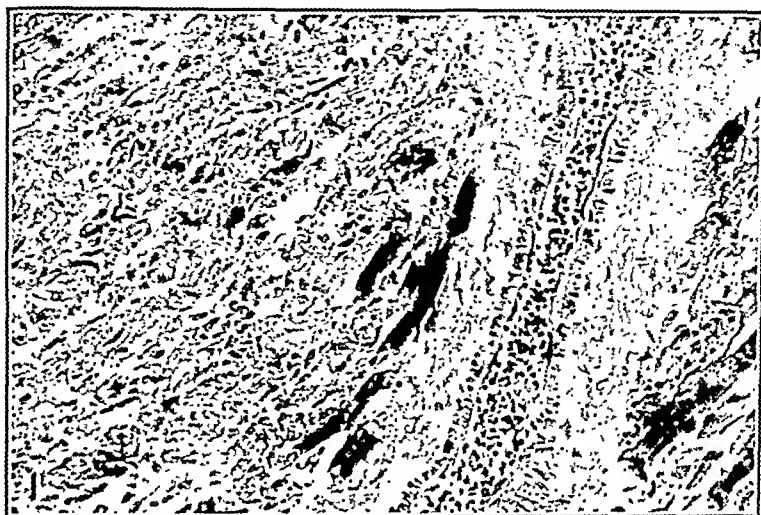


FIG. 1.—AIP Acc. 136990—heart muscle 11 days after the onset of diphtheria. The degenerated fibers have lost their form and are represented by granular amorphous material. The cellular inflammatory reaction is scant at this stage. (Neg. 93109 \times 230.)



FIG. 2.—AIP Acc. 152452—after 19 days, the necrotic muscle fibers have been destroyed leaving a loose stromal net. The inflammatory cellular infiltrate consists principally of large mononuclear cells, lymphocytes and plasma cells. (Neg. 93107 \times 230.)

hyaline degeneration are much less prominent than at earlier stages. By the end of the third week the residual muscle fibers, especially those bordering areas of

After the third week there is progressive fibrosis replacing the lost muscle. Adjacent to these areas of scarring, myofibrillar hypertrophy and nuclear enlarge-

ment, distortion, and hyperchromatism are striking (Figs. 3 and 4). The cellular infiltrate steadily decreases without any change in its differential pattern. Focal hyaline degeneration becomes increasingly

many of these there are neurologic sequelæ which contribute to the fatal outcome.

Fatty degeneration of the myocardium, present in more than half of the 60 cases studied for this feature by Councilman,

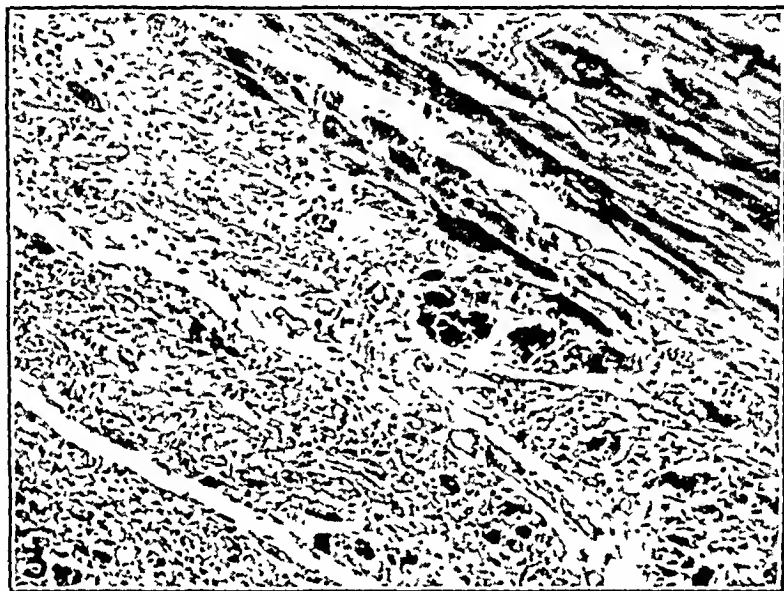


FIG. 3.—AIP Acc. 143672—after 35 days the muscle lesion in the heart shows early fibrosis. A few deeply staining, necrotic fibers may still be seen. (Neg. 93106 \times 160.)

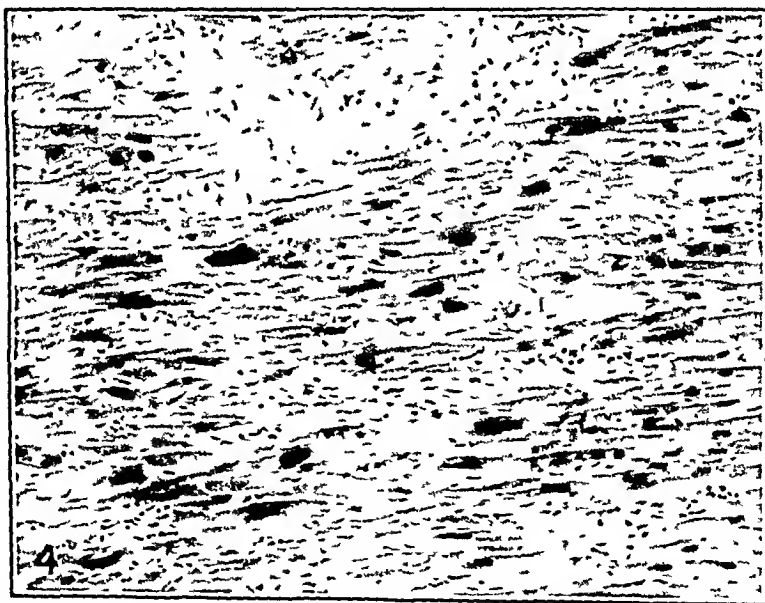


FIG. 4.—AIP Acc. 140532—fibrosis is complete on the 55th day. Note the large, deeply staining, bizarre nuclei of muscle fibers bordering the fibrous areas. (Neg. 93105 \times 160.)

rare; however, it was still noticeable in one case in which death was delayed for 5 weeks. As would be expected, the amount of myocardial damage is less in instances of prolonged survival, but in

Mallory, and Pearce,⁵ was also an inconstant finding in Warthin's²² series and in this study. In many cases large numbers of tiny fat droplets are found in muscle fibers which routine stains show to

have degenerated. In an occasional instance, particularly if death occurs early, fat stains delineate foci of degeneration not apparent in routinely stained sections.

Morphologic changes were not seen in the cardiac nerves included in the sections of myocardium studied.

In brief, it can be said that diphtheritic infection produces a varying degree of parenchymal damage, manifested as segmental hyaline, granular and fatty degeneration of the muscle fibers. The secondary inflammatory response of the stroma appears at first to consist largely of locally developed histiocytes, but it is soon augmented by an influx of plasma cells and lymphocytes. Degenerated muscle is destroyed, leaving gaps and defects in the myocardium, which, if the length of survival permits, heal by fibrosis. The muscle shows only abortive regeneration. Statements by Anitschkow, Heller, and Warthin²² to the effect that there is true muscle degeneration were based on Anitschkow's belief in the myogenic function of the "myocyte," a cell now generally regarded as having a histiocytic function.

Discussion. The figures from clinical studies show a much lower incidence of myocarditis than was found in this post-mortem study. Hoyne and Welford¹¹ reported 496 complicated by myocarditis among 4671 (10.6%) consecutive cases of diphtheria. Kay and Livingood¹² found 7 among 141 (5%) cases of cutaneous diphtheria. The electrocardiograph enabled Burkhardt *et al.*,² to find myocarditis more frequently, since they reported abnormalities in 28 of 140 (20%) consecutive cases of diphtheria. It may be inferred that other methods of clinical diagnosis were less sensitive and were not as accurate a gauge of the true incidence of myocarditis. The presence of abnormalities in each of the cases of this series for which electrocardiograms were made is indicative only of a high degree of selectivity in choosing the patients to be tested. Such a perfect correlation could not have been expected had electrocardio-

grams been taken in all cases in the series. Demonstrable myocardial damage in each of these hearts, nevertheless, is evidence of the value of electrocardiographic studies. Hoyne and Welford¹¹ found a mortality of 62% in the presence of myocarditis in their series, a figure more than five times the 11.6% overall fatality rate in their 4671 consecutive cases of diphtheria. Such a selective mortality serves to explain why myocarditis is found more frequently in post-mortem than in clinical studies.

The modern concept of the pathogenesis of the heart lesion in diphtheria stems from Loeffler's report (1884) that the organism does not extend beyond the local lesion. A few years later, Roux and Yersin isolated the toxin which produces the remote tissue changes. The lesions produced experimentally, as well as those observed in autopsies of human diphtheria, support the statement of Topley and Wilson:²³ "There can be little doubt that the direct action of diphtheria toxin on the heart muscle is one of the most important causes of death." The toxin which is quickly absorbed into the blood rapidly becomes fixed by the tissues, forming a combination which is not broken by the administration of antitoxin.¹⁵ Both functional and morphologic cardiac effects appear early.²³ These characteristics provide the logical foundation for the universally accepted principle of administering antitoxin promptly and in adequate dosage. In this series 132 patients had received diphtheria antitoxin but the available data are inadequate for an analysis of the efficacy of early administration of antitoxin, and, in any case, this point has been so well substantiated in the past that further corroboration is superfluous. Since it has been reported that sulfonamide,⁸ serum,⁴ or other drug^{1,24} sensitivities are capable at times of producing demonstrable myocardial changes, it is interesting that neither the severity, incidence, nor character of the myocarditis was altered by penicillin (98 cases), sulfonamides (86 cases), or serum reactions (9 cases). Though these agents would

have no antitoxic value, neither was there evidence that they contributed to the cardiopathic action of diphtheria toxin.

Neuropathic effects are also a well known sequel of diphtheritic infection. The clinical manifestations are so striking that at one time, as reported in Warthin's²² review, myocardial damage was regarded as secondary to primary nerve injury. Though this concept has been largely abandoned, its occasional resurrection is sufficient reason for comparing myocardial and neuritic effects among the patients of this series. It is to be noted that the numerical and chronologic differences between diphtheritic myocarditis and neuritis depicted in Chart 1 are incompatible with any hypothesis which ascribes morphologic cardiac changes to the nerve injury. Furthermore, other conditions which at times affect the nerves supplying the heart do not duplicate the myocardial changes observed in diphtheria. Among such conditions are poliomyelitis, the Guillain-Barré syndrome and a variety of tumors arising from, or metastasizing in, the region extending from the base of the skull to the upper mediastinum. It seems reasonable to conclude that the myocarditis and neuritis occurring in diphtheria are not causally related to each other.

Although the myocardial changes have been frequently referred to as myocarditis in this report, it should be pointed out that the various authors¹⁶ do not regard a primarily parenchymatous lesion as a true inflammation. However, since inflammation is a biologic response to injury, it seems too fine a distinction to segregate conditions in which injury is morphologically evident from those with more subtle types of cell damage. Histochemical techniques developed within the last few years may provide the means of demonstrating some of these more subtle evidences of cell injury, thus breaking down the artificial distinction between interstitial and parenchymatous inflammation.

The relationship between the myo-

carditic process and cardiac enlargement deserves brief comment. In the medical literature hypertrophy of the heart in "isolated" or Fiedler's myocarditis is often regarded as a feature of that disease.¹⁷ However, since it was frequently present in myocarditis associated with a variety of conditions other than Fiedler's myocarditis or diphtheritic myocarditis¹⁰ its specificity can no longer be given serious consideration. The use of the term hypertrophy, too, is not, strictly speaking, accurate. Increased size and weight is a natural consequence of the inflammatory process within the myocardium; the muscle fibers themselves are not hypertrophied.

Clinically, the deceptive interval of improvement prior to the onset of cardiac dysfunction frequently observed in diphtheria^{15,19} is a characteristic deserving of re-emphasis, especially since it has been found to occur in myocarditis of diverse etiologies.¹⁰ Perhaps, if in diphtheria, myocarditis (or neuritis) were regarded as a sequela to be anticipated as a pharmacologic effect of the toxin, rather than as a complication that develops unexpectedly, a greater proportion of the cases would be recognized early enough to permit adequate remedial measures. Proper therapeutics would recognize the greatly reduced functional capacity of the heart, with the result that the patient's activity would be restricted and great caution observed in the administration of intravenous fluids often and disastrously given in copious quantities to combat a shock-like state which is itself a manifestation of cardiac embarrassment. Proper regard must be given the prolonged convalescence required for healing of the myocardial lesion. Should such measures prove successful in conserving patients with severely damaged hearts, permanent cardiac residua of clinical importance may occasionally result depending upon the quantity of myocardium destroyed. The general denial of permanent clinically significant heart impairment stems from the general failure to save such patients in the past.

Summary. 1. The very high incidence of diphtheria in portions of Europe constitutes a medical hazard to this country under modern conditions of communication.

2. Myocarditis, a frequently lethal sequel, occurred in this series in 143 of 205 (70%) fatal cases of diphtheria. A higher mortality in the presence of myocarditis largely explains why its incidence in post-mortem studies is so much greater than in clinical reviews of diphtheria. A certain proportion of missed diagnoses serves as an additional explanation for this difference.

3. As the length of survival from the onset of diphtheria increases the incidence of myocarditis rises. A similar time relation is true for neuritis. However, post-diphtheritic neuritis appears later and is less frequent than myocarditis. The two sequelae are not related causally to each other. Neither age nor color appear to have any influence upon them.

4. Pathologically, the hearts are dilated, with flabby, pale, or mottled musculature. Frequently the hearts are enlarged, a finding which appears to be related to the presence and degree of myocarditis, and not to myocardial hypertrophy. Micro-

scopically, there is a primary toxic degeneration of the myocardial fibers. The inflammatory response, which culminates in scarring, appears to be secondary to the muscle injury.

5. In one-third of the cases the manifestations of myocarditis appeared at a time when the patient seemed to be well on his way to convalescence. The interval between diphtheria and the onset of cardiac symptoms has been designated the deceptive interval of apparent improvement.

6. The importance of administration of antitoxin early and in adequate quantities is re-emphasized as a measure to prevent myocarditis (and neuritis).

7. The designation of myocarditis (and neuritis) as a sequel of the pharmacologic effect of the toxin rather than as an unexpected complication may contribute to the early and more frequent recognition of myocarditis.

8. A shock-like state following diphtheria must be recognized as a frequent manifestation of myocardial weakness lest the vigorous administration of intravenous fluids to combat it result in a fatal termination.

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STUDIES OF URINARY EXCRETION OF METHIONINE BY NORMALS AND BY PATIENTS HAVING LIVER DISEASE

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WITH the increasing use of methionine in the treatment of diseases in which there is liver damage, the need for further study of the metabolism of this essential amino acid is evident. It is particularly important to establish the degree to which ingested synthetic methionine is utilized by the body, especially for comparison of normals with patients having parenchymatous damage of the liver. While there have been earlier studies of this type, they have been hampered by analytical methods of doubtful validity when applied to biological fluids.

This report deals with the urinary excretion of added dietary dl-methionine by normal children and adults as compared with patients of similar age and weight who showed laboratory or clinical evidence of liver disease.

EXPERIMENTAL. Control assays were made on healthy individuals performing routine hospital duties and eating the customary diet served to hospital personnel. Routine hepatic tests, including cephalin cholesterol flocculation, thymol turbidity, thymol flocculation, and serum bilirubin, gave results for these individuals that were within normal limits.

Patients were chosen for study on the basis of liver damage demonstrable clinically and by laboratory tests. Confirmed diagnoses in this group include 1 case of toxic (aminothiazole) hepatitis and 3 cases of portal cirrhosis.

A group of 6 children being studied for chronic, afebrile disease, whose liver function tests indicated no abnormality, served

as controls. They remained on the customary hospital diet.

Seven children who were suffering from viral hepatitis were studied. One presented frank viral hepatitis. In the remainder there was demonstrable laboratory evidence of liver damage and minimal clinical signs and symptoms. The diagnosis in this latter group was hepatitis without jaundice.

An attempt was made to keep the diets of controls closely comparable to those of the patients. This was facilitated in 12 of the children by the fact that both groups were served indiscriminately from the same food cart.

Dl-methionine was given in the form of 0.5 gm. tablets of "Meonine." For the children aqueous solutions were prepared from chemically pure crystals of the dl-form.*

Urine was collected quantitatively for a control period of 24 hours. Methionine was then given in a single large dose (5 gm. for adults, 3 gm. for children), although it was realized that such administration was unfavorable for maximal utilization. Urine was subsequently collected for three succeeding periods of 24 hours each. Samples were collected in brown bottles containing 20 ml. of 20% HCl, layered with toluene, and stored in a cold room at 4° C.

ASSAY OF METHIONINE IN URINE. The microbiologic assay for methionine developed by Dunn,⁴ adapted for use with oxidized peptone media prepared by the method of Lyman, *et al.*,¹⁰ was used for all analyses. The organism used was Lacto-

* Furnished through the courtesy of Wyeth, Incorporated.

bacillus fermentii—36, which utilizes both the d- and l- forms of methionine. Titratable lactic acid produced by a standard growth of the organism served as an index of methionine present.

Urea, the principal growth-inhibitor (to *Lactobacilli*) found in urine, was removed by treatment of urine with purified urease. Crude urease solution, prepared by extraction of jack bean meal with 15% ethyl alcohol, was dialyzed to remove free amino acids.² Urease treatment of urine was carried out according to the technique of

present in the urine; however, in pathologic urines this possibility cannot be excluded. The finding of wide differences between bound and free methionine at intervals following ingestion of a single large oral dose (of Table 3) supports the hypothesis that the increase is due to liberation of methionine from a simple, hydrolyzable, low molecular compound rather than from a protein complex.

Hydrolysis was accomplished by refluxing urine 6 hours in 6N HCl according to a method previously described.⁸ Again,

TABLE 1.—RESPONSE BY CONTROLS AND BY PATIENTS STUDIED TO HEPATIC TESTS

Patients	Age	Wt. (lbs.)	Diagnosis	Serum bilirubin (mg./100 ml.)	Cephalin chol. flocculation	Thymol turbidity (units)	Thymol flocculation	Col- loidal gold	Col- loidal red	Remarks
Adults:*										
RT . . .	30	150	Normal	1.3	0	2.5	0	±	±	
LB . . .	37	160	Normal	0.77	0	2.0	0	0	0	
JE . . .	26	180	Normal	0.65	0	0.5	0	0	0	
FH . . .	54	170	Cirrhosis	13.3	4+	2.8	3+	3+	..	Biopsy†
PP . . .	52	150	Cirrhosis	0.33	4+	3.0	0	4+	..	
JF . . .	55	135	Cirrhosis	0.10	3+	1.0	0	0	..	Biopsy (2 X)†
BD . . .	13	130	Hepatitis	8.8	4+	5.0	0	2+	..	Diag. porphyria
Children:										
Rh . . .	12	58	Normal	0.32	0	1.0	0	0	0	No bilirubinuria
De . . .	14	65	Normal	0.16	0	0.5	0	0	0	No bilirubinuria
Me . . .	11	72	Normal	0.21	0	1.0	0	0	0	No bilirubinuria
Ho . . .	14	68	Normal	0.42	0	0.5	0	0	0	No bilirubinuria
Dn . . .	15	70	Normal	0.20	0	1.5	0	0	0	No bilirubinuria
Ro . . .	10	52	Normal	0.25	0	1.0	0	0	0	No bilirubinuria
Gu . . .	9	61	Hepatitis	2.13	4+	8.0	4+	4+	4+	Frank jaundice
Ge . . .	15	77	Hepatitis	1.02	3+	0.7	0	±	±	Bilirubinuria
Da . . .	15	67	Hepatitis	1.11	4+	1.5	0	2+	2+	Bilirubinuria
Kr . . .	16	76	Hepatitis	0.67	2+	1.0	0	3+	3+	Bilirubinuria
Mc . . .	15	52	Hepatitis	0.25	0	0.7	0	0	0	Bilirubinuria
Kr . . .	11	50	Hepatitis	0.29	0	0.5	±	0	0	
Ma . . .	14	70	Hepatitis	0.06	0	0.5	0	0	0	

* This individual usually has a slightly elevated serum bilirubin, but repeated liver function tests have given results within normal limits.

† In these cases, the diagnosis was confirmed by needle biopsy of the liver.

Hui Lan Yeh, *et al.*⁸ Standard aqueous methionine solutions subjected to the same steps of urease treatment showed recoveries of 100% (+ 10%). It was found in earlier work that sodium chloride inhibited growth of the *Laetobacilli* used, but under our conditions this effect was negligible up to a concentration of 2% NaCl.

Hydrolysis of urine increases the concentration of methionine found.⁸ This effect was confirmed. In normal urines it is improbable that the increase of methionine values found after hydrolysis is due to liberation of methionine from proteins

standard aqueous methionine solutions subjected to the same treatment showed recoveries of 100% (+ 10%).

It was thought that the increased acidity and browning discoloration (Maillard reaction) produced by autoclaving the assay media might be a source of error. This effect was investigated by assay of Seitz-filtered aqueous standard solutions, urine, and urine with added methionine, in duplicate with the same solutions sterilized by autoclaving 12 minutes at 15 pounds pressure. The results indicate that there was no interference.

Results. Methionine excretion in the control pre-ingestion period, representing the daily basal urinary excretion, is shown in Table 2.

Variations of urinary excretion of dl-methionine after dietary supplement are shown in Figure 1. It will be noted that the amount of dl-methionine found in urine after ingestion of a single dose increased sharply in the first 24-hour post-ingestion period, whereas during the second 24 hours it had returned almost to the control pre-ingestion level. The increased excretion during the first 24 hours represents the portion of ingested dl-methionine which had been absorbed from the gastrointestinal tract and not retained by the tissues. The greatest amount of excreted

given as "Meonine" tablets urine was fractionally collected at convenient intervals. No attempt to establish diuresis was made. Samples were assayed both after urease treatment and after hydrolysis with HCl. The results, listed in Table 3, show that a considerable portion of dl-methionine is excreted in a combined form.

Discussion. The first reported study of urinary excretion of methionine by normal subjects was that of Albanese,¹ who, using a chemical method, found 247 to 494 mg. per 24-hour period. Homburger⁷ employing the same analytical technique, studied methionine excretion by normals, 1 patient with nephrosis, and 2 patients showing evidence of liver damage. He found values of approximately 200 to

TABLE 2.—DAILY BASAL URINARY EXCRETION OF METHIONINE

Normals			Abnormals	
Name	Methionine found mg. per 24 hours		Name	Methionine found mg. per 24 hours
Adults:				
RT	5	8	FH	1 6
LB	4	4	PP	14 5
JW	12	5	JF	9 27
			BD	22 1
Children:				
Rh	1	2	Gu	7 85
De	2	1	Ge	5 4
Me	6	1	Da	6 4
Ho	4	85	Kr	4 8
Dn	8	2	Mc	3 87
Ro	1	86	Kr	2 3
			Ma	5 9

dl-methionine found for the first 24-hour period was approximately 15% of the amount administered, while the average found was approximately 10%.

The patients showing signs of marked liver damage both clinically and by hepatic tests (adult abnormals) exhibited pre-ingestion levels which were higher than in the normals. When these data were subjected to statistical analysis by the chi square method, the differences were found to be of marginal significance. Similar observations were also made in the second post-ingestion 24 hours, indicating delay in return to the pre-ingestion level.

Fractional excretion during a single 24-hour period was studied in one fasting normal. Following a single dose of 3 gm.

400 mg. per 24 hours in the pre-ingestion urines of normals, and values of approximately 200 to 600 mg. per 24 hours in pre-ingestion samples of a patient suffering from hepatolenticular degeneration. He further found an increased excretion by patients showing liver damage given supplementary methionine as compared with normals.

In this study, preliminary analyses based on chemical methods yielded inconsistent results. The method of Albanese,¹ based on the oxidation of methionine by iodine was considered as lacking the necessary specificity for biological fluids. The colorimetric nitroprusside reaction as described by Csonka and Denton³ was investigated, and values found in normal

urine were too low to be either accurate or reproducible. Attempted modifications of this technique to include preliminary treatment for removal of interfering substances (such as histidine and cystine) also failed to give consistently reproducible results.

Harper, Kinsell and Barton have studied plasma and urine levels of methionine after intravenous injection,⁶ using a microbiologic

assay which measured the 1- isomer. Their data show a pre-injection level of 0.1 mg. per hour, and they found that for 3 hours after intravenous injection, 1.6 to 6.5 mg. of an injected 750 mg. were recovered from the urine. Hui Lan Yeh, *et al.*⁸ studied the amino acid excretion in the urine of a patient suffering from congenital cystinuria. Using a microbiologic

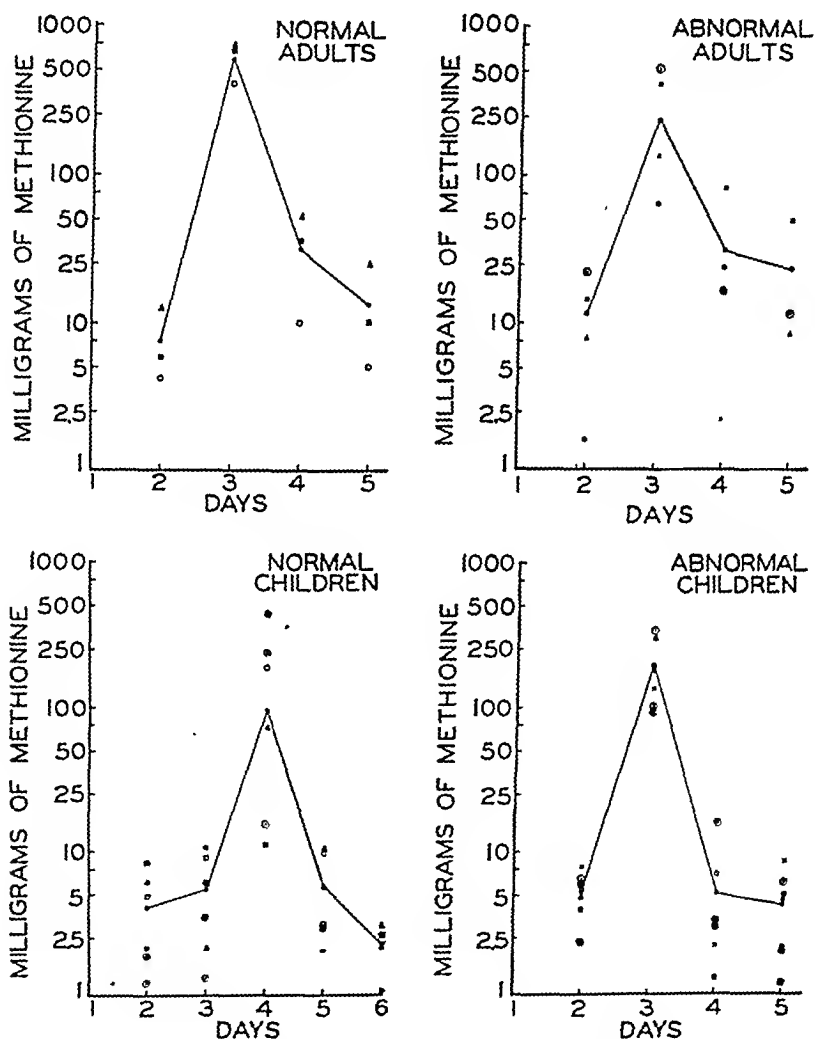


FIG. 1.—Excretion of supplementary dietary dl-methionine by normals and by patients with liver disease. A, The excretions are entered in the graphs at the end of each 24-hour period. Thus, the values shown at 2 days represent the pre-ingestion excretion. Methionine was administered at the beginning of the second day. B, Abnormal (milligrams of methionine found) are plotted on a logarithmic scale. C, Solid circles connected by lines are averages of values found. Each other symbol represents an individual determination on a patient. D, In the chart of "Normal Children" the lowest point represented by a black square corresponding to the 4th day is not included in the average. An unknown, probably major, portion of this 24-hour specimen of urine was lost.

method which measured both d- and l-forms of methionine, they found values of 3–25.5 mg. per 24 hours (mean of 11.03). Subsequently Dunn⁵ has studied the urinary excretion of 12 amino acids by normal subjects using the same method; he found values for methionine averaging 2.7 mg. per 24 hours.

and has reached an average of only 10% of the supplementary dose of methionine given. Thus, it may be assumed that in hepatic conditions methionine may be utilized apparently to the same extent as in normal persons. It seems that the liver damage must be extensive before significant alteration of urinary excretion of exo-

TABLE 3.—FREE AND COMBINED METHIONINE FOUND IN FRACTIONAL SPECIMENS OF URINE COLLECTED IN A 24-HOUR PERIOD FOLLOWING INGESTION OF 3 GM. BY A FASTING NORMAL ADULT SUBJECT

	Fasting	Interval				Total
	8:00 A.M.	1:20 P.M.	5:30 P.M.	11:30 P.M.	8:00 A.M.	
Volume, in ml.	330	345	215	500	595	1655
After urease treatment, dl-methio- nine as micrograms/ml.	9.8	967	405	111	17	
Mg. dl-methionine	3.2	334	87	56	10	487
After HCl hydrolysis dl-methionine as micrograms/ml.	15.3	1045	980	192	52.5	
Mg. dl-methionine	5.0	361	210	96	31.2	698
Ratio, combined/free	1.55	1.08	2.41	1.63	3.12	1.43

The results of this study confirm the latter findings, all of which are based on a microbiologic assay. Consistent recovery of known amounts of methionine added at various steps in the assay procedure confirm the reliability of this method. The fact that smaller amounts of methionine can be detected by, and are found by this method furnishes evidence that the microbiologic assay is more specific than chemical methods. The high values found^{1,7} on chemical determination for normal urinary excretion of methionine (250 to 500 mg. per day) in contrast to the much lower corresponding figures (2.5 to 15 mg. per day) of the microbiologically determined urinary methionine, are due probably to error inherent to the chemical methods in question, when applied in biological fluids.

In one group of patients suffering from hepatic disease the urinary excretion of methionine has shown no significant difference from values found in normal persons. Ingestion of additional methionine in one large dose (3 gm. to children, 5 gm. to adults) has produced both in normal persons and in patients with hepatitis or cirrhosis, a sharp rise in the urinary figures of methionine. However, the total amount excreted was found to be relatively low,

genous (or endogenous) methionine can be found.⁹

Slight prolongation of high methionine levels in the urines of patients suffering from hepatic disease would appear to be the only deviation from excretion by normals. This difference manifested itself only in the group of adults with their more severe hepatic conditions and was not apparent in the group of children suffering from mild hepatitis. Interpretation of this finding must include evaluation of the use of dl-methionine. Although the occurrence of d-amino acids in proteins has been reported,¹² their significance in human metabolism has not been established. Since *Lactobacillus fermentii*-36 measures both enantiomorphs, the isomeric type of the methionine found in these studies remains to be established. It is not unlikely that the increased post-ingestion values represent renal spillover from a transient hyper-d-methioninemia produced by administration of dl-methionine in amounts greater than physiologic needs. This explanation is supported by finding low basal excretion levels, suggesting that methionine is ordinarily almost completely metabolized, even in patients suffering from hepatic disease.

In severe cirrhosis, the absorption of methionine (solution of crystalline dl-

methionine) from the small intestine is slightly impaired, as shown by Machella in this laboratory.¹¹ It is questionable whether this slight delay in absorption represents a satisfactory explanation for the prolongation of high methionine levels in the urine, extending over several days after the ingestion of one dose.

Summary. The urinary excretion of methionine has been studied by means of the microbiologic assay method (*Lactobacillus fermentii*-36) in groups of 3 normal adults, and 6 children as well as of patients of similar age distribution (4 adults and 7 children) suffering from mild or moderately severe hepatic disease (hepatitis,

cirrhosis). One large supplementary dose of dl-methionine produced after ingestion a considerable but transient rise in the urinary excretion of methionine in all groups. However, the relative total amount excreted remained low throughout (approximately 10% of the dose given). Slight prolongation of the high methionine levels in the urine of adults suffering from moderately severe hepatic disease constituted the only difference from excretion by normals.

It is concluded that methionine is well utilized by patients with hepatic disease of mild or moderately severe nature.

Our gratitude is due to John G. Reinhold, Ph.D., for helpful advice and to Miss Jane Joraleman for technical assistance.

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URINARY EXCRETION OF NIACIN AND RIBOFLAVIN IN PATIENTS WITH ACUTE INFECTIONS AND VARIOUS CHRONIC DISEASES*

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THE association of famine with disease has been recognized since the beginning of recorded history. Recently a definite relationship between diet—chiefly the intake of vitamins and proteins—and susceptibility to infection has been shown in numerous animal experiments. This relationship does not appear to be the same for bacteria and viruses; however, it has also been shown that poorly nourished animals are actually more resistant to certain viral infections, particularly poliomyelitis and vaccinia, than are well nourished animals. This difference in susceptibility to bacterial and viral infections may be dependent upon the requirements of the host or invading organism for certain metabolic essentials, as well as upon the localization (intracellular or extracellular) of the parasite. At any rate, it is evident that vitamin deficiencies do not invariably lead to lowered resistance to all infectious diseases, although it is thought that a well balanced diet is important in maintaining a defense against infection and in speeding the recovery from bacterial infections.

THE PROPHYLACTIC ADMINISTRATION OF VITAMINS. Vitamins are often administered to patients on the hypothesis that they may increase their resistance to bacterial infections. This practice has resulted in the indiscriminate use of excessive quantities of expensive vitamin preparations where little, if any, indication for such treatment is present. The disappointing results of such therapy in the prophylaxis of upper respiratory infections and in the

treatment of such conditions as infectious arthritis are familiar to all practitioners.

THE SUPPORTIVE ADMINISTRATION OF VITAMINS. It is usually assumed that during an acute infection or a chronic illness, particularly where fever and disturbances of metabolism are present, the requirements for vitamin substances are increased. Marked evidences of protein catabolism have been demonstrated in Rocky Mountain spotted fever, for example, and it has been shown that this disease can be more successfully managed by the forced feeding of a high-protein diet.⁴ The marked increase in protein and carbohydrate metabolism in such illnesses suggests that the demands for the B-complex vitamins may also be increased. The use of vitamins as supportive therapy in infections and in chronic diseases is still largely empiric, however, particularly in human beings. An estimation of the vitamin needs of ill patients would depend upon the preceding diet and degree of tissue storage, as well as upon the intake, absorption, utilization, and actual requirements during the illness. Such data are rarely available. The importance of niacin and riboflavin in the metabolism of carbohydrates and amino acids would seem to indicate that these vitamins have vital rôles in promoting recovery from injury and infection.

THE RECOGNITION OF VITAMIN DEFICIENCIES. It is generally agreed that for each case of a severe deficiency state recognized by clinical means alone, many

* This study was aided by a grant from the John and Mary R. Markle Foundation.

instances of mild deficiencies probably exist. Attempts at evaluating such states of nutrition are difficult, and, as a result, concepts of deficiency diseases have been somewhat confused: the clinicians state that frank evidences of dietary deficiencies are growing less common, while the nutritionists continue to maintain that routine surveys reveal marked evidences of inadequate diets. The recognition of mild vitamin deficiencies by clinical examination alone is often difficult, if not impossible. A gradual depletion of body reservoirs, with subsequent lowering of the concentration of vitamin substances in the blood and urine, precedes functional disturbances, microscopic tissue changes, and gross anatomic changes.

The development of laboratory procedures for the purpose of measuring vitamin substances in the urine and estimating body stores by the use of a test dose of vitamins appears to offer a means of determining actual vitamin needs. Previous studies have shown that the results of these laboratory tests correlate well with the physical evidences of deficiency states.¹⁰ In an effort to obtain more accurate information concerning the nutritional states and requirements of patients with acute and chronic illnesses, the present study was undertaken to determine the amounts of niacin and riboflavin excreted in the urine of hospitalized patients who had acute infections and various chronic diseases.

SELECTION OF PATIENTS AND METHOD OF STUDY. Three groups of hospitalized patients were studied. Group 1 consisted of 13 patients with acute infections such as streptococcal pharyngitis, acute rheumatic fever, Rocky Mountain spotted fever, pyelitis, and pneumonia. Convalescence in these patients was usually noted by the end of the second or third week. Group 2 consisted of 68 patients with prolonged or chronic illnesses, such as heart disease, peptic ulcer, syphilis, chronic pulmonary disease, and chronic pyogenic infections. Group 3, which served as a control, was made up of 22 hospitalized

patients who had no evidence of organic disease.

None of the patients studied had received any previous vitamin therapy. During the period of study all patients were given a bland diet containing 1800 to 2000 calories daily, divided as follows: protein, 60 to 70 gm.; fat, 80 gm.; carbohydrate, 100 gm. This diet was estimated to contain 2.9 mg. of riboflavin and 12.7 mg. of niacin.

Determinations of niacin and riboflavin were made on urine collected in dark-brown glass bottles for protection against light. Glacial acetic acid and toluol were used as preservatives. Three consecutive 24-hour collections of urine were made, the amounts of niacin and riboflavin contained in each were determined, and the results of the determinations were averaged. On the morning of the fourth day, 5 mg. of riboflavin and 50 mg. of niacinamide were given orally with breakfast, after which a 3-hour urine collection was made.

The niacin assays were done by the method of Perlzweig⁵ for the determination of urinary F_2 (N-methylnicotinamide). The riboflavin levels were determined by the direct fluorometric method of Ferrebee, omitting the absorption and elution steps.³

Results. The urinary levels of niacin and riboflavin for the various groups are seen in Tables 1 and 2. Before the administration of a test dose of niacinamide, little difference in the amount of F_2 excreted was noted between Group 3 (controls) and the other groups studied. The slightly higher urinary levels of F_2 in the groups with acute infections and cancer were not found to be statistically significant.

Following the administration of 50 mg. of niacinamide, the amount of F_2 excreted by the patients with acute and chronic infections was higher than that excreted by the controls. The difference was subjected to statistical evaluation by the "t" test and was found to be significant.*

The urinary excretion of riboflavin did not vary significantly in any group except in the patients with peptic ulcer. Here, as

* Statistical analysis was done by Dr. C. N. Herndon of the Division of Medical Genetics.

might be expected, where the previous diet had, in most instances, been rich in sources of riboflavin (milk and cereal), the levels of urinary riboflavin before and after the test dose were 20 to 25% higher than those in the control group.²

ies does not support such a belief and the facts do not justify such a conclusion.

LIBERATION OF VITAMINS FROM STORAGE DURING ILLNESS AND STARVATION. It is possible that increased amounts of these vitamin substances are liberated

TABLE 1.—URINARY EXCRETION OF NIACIN

	No. cases	Before test dose		After test dose	
		Range (mg.)	Mean (mg.)	Range (mg.)	Mean (mg.)
Group 1:					
Acute infections	13	3.9-11.7	8.5	4.0-14.2	7.1*
Group 2:					
Chronic diseases	83				
Cancer	15	4.6-13.9	8.4	1.1-8.2	3.7
Pyogenic infection	4	5.6-10.5	9.0	3.7-12.1	6.8*
Syphilis	4	1.9-17.6	7.0	1.6-6.9	3.6
Lung disease	3	6.3-7.4	6.9	3.1-5.8	3.7
Heart disease	17	2.9-14.8	6.9	0.6-10.1	3.8
Peptic ulcer	25	3.2-15.5	6.7	1.1-15.2	4.6
Miscellaneous	15	1.2-11.9	4.2	0.5-11.0	4.0
Group 3:					
Controls	22	2.5-12.2	7.2	1.0-6.7	2.9

* Statistically significant.

TABLE 2.—URINARY EXCRETION OF RIBOFLAVIN

	No. cases	Before test dose		After test dose	
		Range (γ)	Mean (γ)	Range (γ)	Mean (γ)
Group 1:					
Acute infections	13	674-6393	1682	440-3128	2194
Group 2:					
Chronic diseases	83				
Cancer	15	475-2512	1246	532-4268	1708
Pyogenic infection	4	994-2573	1645	908-2550	1597
Syphilis	4	944-2009	1490	464-2288	1761
Lung disease	3	1212-2260	1738	816-2380	1851
Heart disease	17	576-4595	1621	1302-3488	2026
Peptic ulcer	25	622-6311	2003	520-4830	2421
Miscellaneous	15	712-2640	1440	424-3720	2172
Group 3:					
Controls	22	640-4224	1482	232-6771	2025

Discussion. In evaluating the results of the present study certain apparent discrepancies are noted. The quantity of niacin and riboflavin excreted by ill patients, contrary to what might be anticipated, is as great or greater than that excreted by the controls. While this finding might be interpreted to indicate that the nutritional state of the former patients was better than that of the latter, the evaluation of their previous dietary history

from storage incidentally, or perhaps as a protective mechanism, by fever, an increased rate of metabolism, and tissue destruction. It would appear that until the body reserves are depleted, excretion of these substances at the onset of an illness may actually be greater than normal. In healthy subjects on a voluntary fast relatively normal urinary levels of niacin have been found.⁷ In addition, the work of Meehelson and Erickson with normal

subjects has shown that urinary F_2 (N-methylnicotinamide) levels, even after periods of restricted diet, are maintained for a period as long as 32 days, with only a slight decrease. The niacin and riboflavin excreted by such persons are apparently derived from the tissues which contribute the urinary nitrogen.

The normal or elevated urinary levels of F_2 and riboflavin found in Groups 1 and 2 suggest the following conclusions:

That in most instances the amounts of niacin and riboflavin stored in the tissues appear to be adequate to supply the requirements of patients studied during fairly long periods of illness before gross anatomic tissue changes appear; this assumption would account for the relative infrequency of frank clinical deficiencies even during prolonged illness.

That during illness, particularly when fever and weight loss are present, normal or increased amounts of riboflavin and niacin may be excreted until the body stores become depleted. Thus it can be understood why frank deficiencies, though they are uncommon even during relatively prolonged illness, are more likely to appear in patients with chronic diseases, since their stores are being more rapidly depleted.

THE RÔLE OF THE LIVER. Another possible factor in the normal to increased excretion of F_2 by ill patients may be the inability to metabolize N-methylnicotinamide in the presence of liver damage. The liver is apparently the chief, if not the sole, organ responsible for the methylation of niacinamide.⁶ N-methylnicotinamide is further broken down by the liver to unknown products. Experimental carbon tetrachloride poisoning in rats diminishes the capacity of the animals to destroy N-methylnicotinamide.⁸ A similar effect has been noted in human patients with liver disease⁴ as well as in apparently normal females during pregnancy.⁹

While the urinary level of F_2 aids in the

evaluation of an individual's nutritional state, it would appear that it also serves as a measure of his ability to methylate and metabolize niacinamide. It is possible that in the presence of infection, particularly where liver function is disturbed, there is interference with the latter process. The highest urinary F_2 levels were found in a patient with Rocky Mountain spotted fever who had evidence of severe disturbance of liver function.

APPLICATION TO THERAPY. It is difficult to say whether or not the increased urinary excretion of niacin demonstrated in patients with acute and chronic infections indicates a need for increased vitamin intake. Where recovery occurs before the body stores are depleted, a satisfactory adjustment is apparently made during convalescence. Since the retention of some of the members of the B complex may be dependent upon the storage of protein, it might be advantageous to supplement the niacin and riboflavin intake following illness. In most instances, the amounts employed (5 to 15 mg. of riboflavin and 50 to 150 mg. of niacin) appear to be considerably larger than necessary. Further study of these aspects of the problem is in progress.

Summary. Assays of the urinary excretion of niacin and riboflavin in hospitalized patients having acute and chronic illnesses differ little from those in a control group of patients, without organic disease. Following the administration of a test dose of these vitamins, the amount of F_2 excreted by the patients with acute and chronic infections is significantly increased. The normal or increased levels in such patients are probably dependent upon liberation of niacin from storage as a result of fever, increased metabolism, and tissue destruction. The increased excretion of F_2 may also be related to disturbance of the liver function and to a diminution of the liver's capacity to metabolize N-methylnicotinamide.

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GANGRENE OF THE EXTREMITIES OF VENOUS ORIGIN

REPORT OF A CASE

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THE common clinical course of the occlusion of the main vein of an extremity is well known. The absence of anoxemia of the tissues in thrombophlebitis or phlebothrombosis is explained by the ease with which the collateral circulation is re-established, due to the abundant venous pathways.

When, however, in addition to the main vein, all the tributaries are also occluded, marked anoxemia of the tissues leading to gangrene may ensue from the sole obstruction of the whole venous tree.

Gangrene, as a result of thrombophlebitis without arterial occlusion is, however, of rare occurrence. Only a small number of such cases have been reported.¹ In the American literature there is only 1 paper; it reports 3 cases.⁸ The possibility of gangrene due to venous obstruction alone is therefore not widely known. Because of the rareness of the condition we wish to report the following case.

Case Report. M. L., 62 years old, white male, was admitted on May 26, 1946, to the Alexian Brothers Hospital, Elizabeth, N. J., for neoplasm of the bladder. The patient had hematuria for about 2 months prior to his admission. Except for a right inguinal hernia and some degree of chronic bronchitis, the patient's general condition was good. At the time of his admission an electrocardiogram was normal and the blood pressure was 150/70. On May 27, 1946, a mid-line suprapubic cystotomy was performed (by Dr. Irving Lerman). The tumor was resected and 5 radon seeds of 1.5 m.c. were inserted. The patient was ambulatory 48 hours after the operation.

On the 4th postoperative day, the patient developed hiccoughs, for which he received

carbon dioxide. Three days later congestion of the right lower lobe was diagnosed and confirmed by a Roentgen ray plate the following day. The patient was running a low fever (101° F.) but there was no tenderness along the lower extremities. He was started on 20,000 units penicillin every 3 hours. On June 7 the left calf appeared infiltrated and tense. The diagnosis of thrombophlebitis became apparent. The patient was then put on dicumarol with 100 mg. as an initial dose, papaverine gr. $\frac{1}{2}$ was given subcutaneously every 4 hours and the leg was elevated. During the following 3 days the calf was distinctly tense and the foot was warm. The patient's general condition was good.

On June 11 (15th postoperative day) at 5 P.M. the patient experienced a sudden pain in the left leg and foot, more marked in the latter. Upon examination, the entire left lower extremity, from the hip down, was swollen and warm, with the exception of the foot and lower third of the leg, which were cold and mottled. The circumference at the calf was 38.5 cm. as against 32 cm. on the opposite side. The dorsalis pedis and the posterior tibial arteries were felt and of good volume. Oscillometric readings were:

	Ankle	Calf
Left	2.5	3.5
Right	2.25	3.5

A paravertebral block with 1% novocaine was performed at L₁, L₂, L₃, and L₄, with good immediate results. The severe pain, present before the block, subsided and the patient remained comfortable during the next 24 hours. Nevertheless, the following day, all the toes appeared much more cyanotic than on the previous examination. Another paravertebral block with novocaine was performed with immediate good results. Despite that, within the next 24 hours, the first and fifth toes appeared completely

black, while the second, third, and fourth ones were black only distally. The areas of gangrene, involving the toes, were more marked on the plantar region. In addition, the ball of the foot and a circumscribed area near the heel also appeared gangrenous (Fig. 1). Two days later, another block was performed with the same apparent favorable response. The patient was much more comfortable. A line of demarcation became evident 4 to 5 days after the onset of gangrene.

the lower extremity had completely subsided, and the gangrene of the left 5 toes was dry and well demarcated. No active surgery was contemplated, for it was assumed that spontaneous amputation would eventually occur. Indeed, the lesions of the ball and heel remained superficial and separated in a few months. As to the toes, after the demarcation between the normal and dead tissues began, the separation of the gangrenous distal phalanges took several

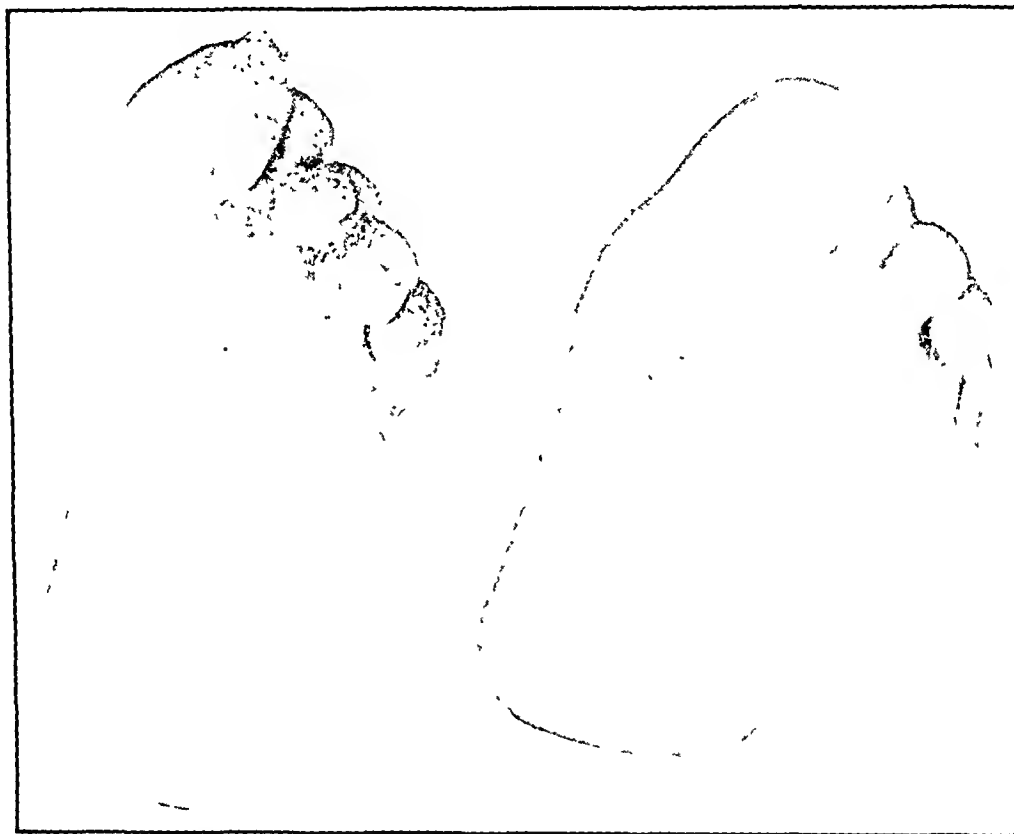


FIG. 1

FIG. 2

FIG. 1.—Plantar region of left foot. Gangrene involving the 5 toes. Additional superficial necrotic lesions are present on the ball of the foot and near the heel.

FIG. 2.—The healed stumps of the 5 toes after spontaneous amputation, 11 months after the onset of gangrene.

On June 19, the circumference at the calf was 33.5 cm. (5 cm. less than 8 days previously). The edema of the entire left lower extremity was subsiding. The areas of gangrene on the plantar region (ball and heel of the foot) showed some fading, while those of the toes remained unchanged.

On July 1 (3 weeks after the onset of the acute ischemic episode) the patient was allowed to be out of bed, and 6 days later he was discharged from the hospital. His general condition was good. The edema of

months (from October 9, 1946, to February 3, 1947). The stumps (Fig. 2) of the different toes were completely healed in May, 1947, 11 months after the onset of gangrene.

While at home, on September 2, 1946, 2 months after his discharge from the hospital, the patient developed a typical ilio-femoral thrombophlebitis of the right lower extremity. The entire limb was markedly swollen, hot and painful. The patient was running a fever of 101.5° F. The next day a right paravertebral block was performed and re-

peated 24 hours later. Within 24 hours after the last block the temperature became normal and the pain subsided. The edema of the extremity subsided within a week. Unlike the thrombophlebitis of the left lower extremity, that of the right side was not accompanied by ischemic phenomena and followed a normal course.

When last seen in June, 1947, all pulses were present in both feet, and the oscillometric readings were normal. It is to be emphasized that throughout the entire course of the disease the foot arteries remained patent and the oscillometric readings were normal.

Discussion. The clinical course of the case we have observed went through 4 distinct phases. *First phase:* at the inception, during the first few days, the thrombophlebitic process appeared as a typical phlegmasia alba dolens. *Second phase:* on the 5th day the patient experienced a sudden pain and his left leg and foot became cold and cyanotic. The clinical picture took the aspect of a phlegmasia cærulea dolens or blue thrombophlebitis. *Third phase:* 3 days later, the toes and 2 areas of the plantar surface became gangrenous. *Fourth phase:* regression and demarcation of the lesions began 4 to 5 days after the onset of gangrene. The spontaneous amputation of the 5 toes and the healing of the plantar lesions required several months. At present there are no post-phlebitic sequelæ and the walking capacity of the limb is normal.

DIAGNOSIS. The first 3 stages are typical of the course of a thrombophlebitis resulting in gangrene. At the second and third phases, however, it may be difficult to differentiate between an acute venous and arterial occlusion. Indeed, a syndrome characterized by a sudden onset of pain, cyanosis and coldness of an extremity, as seen in the second phase, may correspond either to an acute blue thrombophlebitis or to an acute arterial occlusion. In our case the presence of edema and the patency of the foot arteries were in favor of the former diagnosis. In certain instances arterial spasm may accompany the onset of the venous occlusion, in which

case the latter is easily mistaken for an arterial embolism.^{2,5} The use of intravenous papaverine or a paravertebral block may be of great help in the differentiation of these 2 conditions. In some cases with prolonged spasm the true nature of the occlusive vascular syndrome has been established only during surgical exploration of the main vessels.^{5,6,7}

At the third phase, the examination of the pulses and the oscillometric findings are decisive in establishing the diagnosis. The patency of all the arteries and normal oscillometric readings should rule out the diagnosis of gangrene due to arterial or mixed arteriovenous occlusion.

The prognosis of post-phlebitic gangrene is usually poor. In most of the instances recorded in the literature, leg or thigh amputation was required. A favorable outcome, as seen in the present case, is of rare occurrence. Another such instance in which there was only minimal loss of tissues (spontaneous amputation of the toes) was also reported by Fontaine and Forster.³

PATHOGENESIS. Gangrene of venous origin is a distinct clinico-pathologic entity. Clinically the venous syndrome is a blue thrombophlebitis, resulting in gangrene. Careful dissection of the amputated limb, or at autopsy, reveals an extensive occlusion of the whole venous system (main vein and its tributaries) and the absence of any organic lesion of the arterial tree. Experimentally⁴ it has been shown that this type of gangrene could be reproduced in the animal, provided the blockage of the venous system is complete.

Since in some cases there is evidence of arterial spasm accompanying the thrombophlebitic process, the question arises as to how much it is responsible for the gangrene. From the available data, arterial spasm appears to play rather a minor rôle if any, in its causation. Our present case supports this view, since at no time during the course of the disease was there any evidence of spasm.

As to the mechanism, the clinico-pathologic and experimental data seem to

indicate that, although the arterial blood could reach the tissues, its return is prevented by the blockage of the venous system, leading thus to stasis and anoxia of the tissues, resulting in gangrene.

TREATMENT. From a therapeutic standpoint, it is obvious that the management of this condition will vary according to the phase. In the beginning, at the phlegmasia cærulea dolens stage, the use of papaverine and/or paravertebral block of the sympathetic ganglia and anticoagulants should prove effective against the angiospasm and further extension of the venous thrombosis.

When gangrene sets in, and the diagno-

sis of its venous origin is certain, it is important to remember that the necrosis may remain superficial. Delaying amputation seems therefore indicated, unless signs of toxemia are present.

Summary. 1. A case of gangrene of the lower extremity due to venous occlusion is reported.

2. The clinico-pathologic characteristics of this type of gangrene, namely, extensive thrombosis involving all the veins and patency of the arterial system, are described.

3. Pertinent therapeutic indications are stressed.

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IN VIVO STAINING AND RETARDATION OF TUMORS IN MICE BY ACRIDINE COMPOUNDS*

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In previous studies¹⁴ (1946) it was shown that acridine dyestuffs of Colour Index No. 788 added to the diet of tumor bearing mice stained sarcomata and spontaneous carcinomata and retarded their growth. In addition to 36 commercial dyestuffs studied at that time, 34 acridine compounds synthesized as antimalarials‡ were tested on tumor bearing mice, and, five were found that stained and retarded tumors in mice.

Acridine compounds have been extensively synthesized and studied as dyestuffs, antibacterial and antimalarial agents. Reviews on the latter two aspects have been furnished by Albert, Rubbo, Goldacre, Davey and Stone¹ (1945); Martin¹⁷ (1944); and Wiselogle²² (1947).

Through the generous collaboration of Dyestuff Manufacturers and of Laboratories§ which synthesized compounds for studies on Malaria, we were able to obtain samples, together with information regarding their structural formulæ, solubility, and when known, their toxicity, for our studies on the structural nature of compounds that stain and retard tumors in mice. The results of these investigations

which include 296 acridine antimalarials and 50 dyestuffs are reported in the present communication.

Material and Method. The mice used were 40 to 50 days old inbred Bagg albino (our own) and C57 black strains (our own), weighing 18 to 20 gm. bearing transplanted sarcomata, (BA, No. 1 and C57, No. 241, originally induced by means of 1:2:5:6-dibenzanthracene), and mice of the dilute brown, J. W. Thompson's C3H, and inbred albino strains bearing spontaneous mammary gland carcinomata.¶ In some experiments mice of the Andervont C3H strain ingrafted with a carcinoma that arose spontaneously in a mouse of this strain were also used.

The acridine antimalarial compounds were ground together until pulverized with Purina fox chow meal in amounts equivalent to 0.1 and 0.15%, the dyestuffs to 0.4%, of the food weight. These relatively large amounts were administered in order to establish their maximum staining and retarding action on tumors and their toxicity to mice. Diets containing 25 different compounds were prepared and placed in amber glass jars with tight screw tops. Thirty mice of an inbred strain were then implanted subcutaneously with a measured small graft (5 x 2 x 1 mm.) of a 100% transplantable

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§ Abbott Laboratories, North Chicago, Ill.; Calco Chemical Division, American Cyanamid Company, Bound Brook, N. J.; Ciba, Ltd., Basle, Switzerland; The Dow Chemical Company, Midland, Mich.; E. I. duPont de Nemours & Co., Jackson Laboratories, Wilmington, Del.; Durand & Huguenin, S. A., Bâle, Switzerland; General Dyestuff Corporation, Philadelphia, Pa.; Hartman-Leddon Company, Philadelphia, Pa.; Imperial Chemical Industries, Manchester, Eng.; The Lilly Research Laboratories, Eli Lilly & Company, Indianapolis, Ind.; Marietta-Harmon Chemicals, Inc., Marietta, Ohio; William S. Merrell Company, Cincinnati, Ohio; The National Drug Company, Philadelphia, Pa.; New York Color and Chemical Company, Belleville, N. J.; Nyanza Color and Chemical Company, Brooklyn, N. Y.; Parke Davis & Company, Research Laboratories, Detroit, Mich.; Pharma Chemical Corporation, Bayonne, N. J.; Squibb Institute, New Brunswick, N. J.; Sterling-Winthrop Research Institute, Renens, N. Y.; The Upjohn Company, Kalamazoo, Mich.

¶ Presented to us from the Research Department of the Lankenau Hospital, Philadelphia, Pa.

sarcoma native in the strain used, placed in individual containers and given 3 to 5 gm. of food each (i. e. slightly more than the amount utilized by a normal mouse); 24 of them receiving treated and 5 untreated chow. Records of food intake were not made.

Samples of urine were examined, and the mice were sacrificed about 14 days later by which time those receiving untreated food were ill or moribund with large tumors. The treated mice were sacrificed at this time because sufficient quantities of only a few of the compounds were available for longer studies.

As each mouse was sacrificed records were made of its condition and of the size and color of its organs and tumor. If the mouse had grown well (mice were not weighed), was in good condition, and its tumor was large and uncolored, the test was not usually repeated. Tests on mice that became ill or did not grow were repeated using less compound. Compounds that stained and retarded sarcoma were tested on mice bearing spontaneous mammary gland adeno-carcinoma.

The acridine compounds tested numbered 331; 27 had no amino group, 269 had one amino group and 35 had two amino groups situated upon the acridine structure. Of the mono-amino and di-amino compounds 204 stained tumor tissue. The majority of the compounds that stained tumor tissue brought about some retardation of its growth.

Results. Acridine Dyestuffs. The results of our studies on acridine dyestuffs were the same as those previously reported, namely, dyestuffs of Colour Index No. 788 stained and retarded tumors in mice; those of other Colour Index numbers failed to stain tumors. Many dyestuffs were toxic in concentrations equivalent to 0.4%, the amount used in our earlier studies with commercial dyes, but not in 0.2%. Samples of acridine orange were purified by the American Cyanamid Company (Calco) and E.I. duPont de Nemours & Company to see whether the toxicity of commercial dyes might be due to the presence of impurities.

Acridine Antimalarials. Oral administration of 49 of them, in amounts equivalent to or less than 0.15% dry weight of their food, resulted in stained tumors that

were smaller than those in untreated mice of the same series; 16 of them retarded the growth of tumors to such an extent that they were 1/20 to 1/40 the size of those in the controls (Table 2).

The majority of the 127 compounds that failed to stain tumor tissue, also failed to retard its growth and only a few resulted in unstained tumors that were less than 1/10 the size of those in untreated mice of the same series (Table 3).

A few of the compounds brought about marked retardation of tumor growth even when administered in low concentration, 0.05% to 0.03%. These were WIC-37, WIN-340, and WIN-501 (see Tables 2 and 3). Although these compounds were toxic when fed in amounts equivalent to 0.1%, when used in lower concentrations the treated mice remained healthy.

Many of the compounds were excreted in bile and urine. Colored urine did not necessarily mean that the animal's tumor would be colored; on the other hand, tumors were not stained in animals whose urine was normal in color.

As mentioned in previous studies¹⁴ (1946) staining of tumor tissue by compounds given by mouth results in diffuse coloration throughout the tumor tissue and is not located in granules in tumor cells, in cells of necrotic areas or in cells of adjacent tissues.

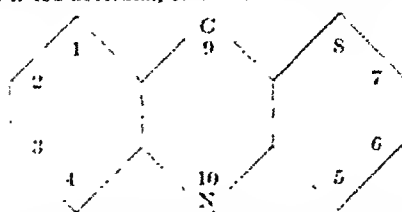
The lymph nodes, thymus, testicle and intestinal walls of mice in which tumor tissue was stained were also diffusely stained a paler tint of the same color and in a few the medulla of the adrenal was diffusely stained. In addition to this diffuse staining, darker yellow granules were found in epithelial cells covering intestinal villi, in macrophages within villi, in cells of a few collecting tubules of the kidney, and in cells composing the kidney medulla. The liver was yellow in mice that received certain of the compounds.

Some tumors were pale yellow (WIC-27), some bright yellow (ERS-343), and some orange color (A-79). The intensity of the growth retarding action was not associated with the color brought about in the tumor.

TABLE 1. STAINING RESULTS WITH THE VARIOUS COMPOUNDS TESTED

No amino group	No.	Stained	Unstained
9, 10-position substituents	16	0	16
2-methoxy-9, 10-position substituents	1	0	1
3-chloro-9, 10-position substituents	1	0	1
1,2,3,4-tetrahydro-9, 10-position substituents	1	0	1
2-methoxy-6-chloro-9-position substituents	6	0	6
2-methoxy-6-chloro-9, 10-position substituents	1	0	1
	26	0	26
Monoamino	No.	Stained	Unstained
9-amino	6	3	3
2-chloro-9-amino	1	1	0
3-chloro-9-amino	3	2	1
4-chloro-9-amino	2	0	2
2-methoxy-9-amino	2	1	1
4-methoxy-9-amino	1	1	0
2-methyl-9-amino	1	0	1
4-methyl-9-amino	3	1	2
Benzo(a)-9-amino	3	2	1
Benzo(e)-9-amino	3	2	1
Benzo(a)-6-chloro-9-amino	1	1	0
3-phenyl-imino-9, 10-position substituents	1	0	1
2-bromo-4-methyl-9-amino	1	1	0
2-chloro-4-methyl-9-amino	1	0	1
3-chloro-4-methyl-9-amino	1	0	1
3-chloro-5-methyl-9-amino	1	1	0
2-methoxy-4-chloro-9-amino	1	0	1
3-nitro-6,7-dimethoxy-9-amino	5	3	2
2-hydroxy-6-chloro-9-amino	1	0	1
2-methoxy-6-chloro-9-amino	212	153	54
2-methoxy-7-chloro-9-amino	2	1	1
2-methoxy-6-cyano-9-amino	5	4	1
2-methoxy-6-methyl-9-amino	1	1	0
1-methyl-4-methoxy-9-amino	1	0	1
3,6-dichloro-9-amino	1	1	0
3,6-dichloro-4-methyl-9-amino	1	1	0
4,6-dichloro-2-methoxy-9-amino	1	1	0
6-chloro-2,3-dimethoxy-9-amino	1	1	0
9-(para-amino)phenyl-3-amino	6	0	6
9-(para-amino)phenyl-7-methyl-3-amino	1	0	1
	270	187	83
Diamino	No.	Stained	Unstained
3,6-diamino	2	0	2
3,6-dimethylamino	16	16	0
3,6-diacetylamino	1	0	1
10-methyl-3,6-diamino	4	0	4
9-phenyl-3,6-dimethylamino	1	1	0
2,7-dimethyl-3,6-diamino	4	0	4
2,7-dibromo-3,6-diamino	1	0	1
2,7-dimethyl-9-phenyl-3,6-dialkylamino	5	0	5
2,7,9-trimethyl-3,6-diamino	1	0	1
	35	17	18
Total	331	204	127

The compounds tested were listed according to the German scheme of classification:



(The acridine structure is so numbered that the *meso* carbon atom is at position 9. However, according to the manner of counting around the ring, similar compounds came differently named; for instance, 2-methoxy-6-chloro-9-amino acridine, or 7-methoxy-3-chloro-9-amino acridine.)

The amount of these compounds available for our studies was too small, in most instances, to permit studies on survival time of normal and of tumor bearing mice so that studies on prolonged feeding were not attempted. A few records were made,

however, on the size of tumors in mice treated longer than usual. These showed that D-91, D-92, D-94, WIC-1, WIC-22, WIN-146, A-66 and quinacrine could be fed to tumor bearing mice for over a month in amounts that markedly retarded

TABLE 2.—RESULTS WITH STAINED TUMORS AND ONE-TWENTIETH TO ONE-FORTIETH THE SIZE OF THOSE IN UNTREATED MICE

Compound	Source	Size of tumor (c.mm.)	No. of days
3-chloro-7-methoxy-9-[γ -(β' -diethylamino-ethylthio)propylamino]acridine, di HCl	Sterling-Winthrop WIN-340	100	14
9-(ω -n-piperidylamylamino)-3,4-benzoacridine, 2HCl	Parke, Davis WIC-37	120	14
9-(4-dimethylamino-cyclohexylamino)-7-methoxy-3-chloro-acridine, 2HCl	Merrell 192R-92	200	14
2-bromo-4-methyl-9-(δ -diethylamino- α -methyl butylamino) acridine, di HCl	Lilly ERS-343	240	14
3-chloro-9-[γ (ethyl- β -hydroxyethylamino-propylamino)]-7-methoxy-acridine, 2HCl	Parke, Davis WIC-12	256	15
2-methoxy-6-chloro-9-(1'-n-propylisopropylamino-4'-pentylamino) acridine, di HCl	Lilly A-79	300	16
2-methoxy-6-chloro-9-(1'-ethyl-n-propylamino-4'-pentylamino) acridine, di HCl	Lilly A-85	300	15
4-methyl-9-(δ -diethylamino- α -methyl butylamino) acridine, di HCl	Lilly ERS-340	340	15
2-methoxy-6-chloro-9-(4'-dimethylamino-anilino) acridine	Parke, Davis WIC-27	350	15
6-chloro-2-methoxy-9-(4-dimethylamino-butylamino) acridine, dihydrochloride	Sterling-Winthrop WIN-501	350	14
2-methoxy-6-chloro-9-(2'-diethylamino-4'-butylamino) acridine, di HCl	Lilly A-55	360	15
γ -(2-methoxy-6-chloro-9-acridylamino) propyl- β -di-ethylamino-ethyl sulfide, 2HCl	Parke, Davis WIC-42	360	14
2-methoxy-6-chloro-9-(1'-ethyl-isopropylamino)pentylamino acridine, di HCl	Lilly A-172	420	14
3-chloro-7-methoxy-9- γ -dibutylamino-propylamino-acridine, 2HCl	Parke, Davis WIC-25	432	15
2-methoxy-6-chloro-9-3-ethylamino-propylamino) acridine, HCl	Abbott D-91	480	15
Atabrine dihydrochloride	Marshall 225	455	14

Control mice died with tumors about 8000 to 11,000 c.mm. at 14 to 16 days.

TABLE 3.—RESULTS WITH UNSTAINED TUMORS AND ONE-TENTH TO ONE-FORTIETH THE SIZE OF THOSE IN UNTREATED MICE

Compound	Source	Size of tumor (c.mm.)	No. of days
6-chloro-2-methoxy-9-[γ -(γ -aminopropylamino)propylamino] acridine, citrate	Parke, Davis WIC-30	144	15
9-(4-dimethylamino-cyclohexylamino)-6,7-dimethoxy-3-nitro-acridine, 2HCl	Merrell 192R-190	248	14
6-chloro-2-methoxy-9-[γ -(4'-diethylamino-phenylamino)propylamino] acridine, 2HCl	Parke, Davis WIC-23	480	15
9-(δ -diethylamino- α -methyl) butylamino-acridine, di HCl	Lilly ERS-334	600	18
2-methoxy-6-chloro-9-cyano acridine	Lilly J-143	960	17
2-methoxy-6-chloro-9- γ -n-(pipecolino propylamino) acridine, di HCl	Lilly A-27	960	13
6-chloro-9-(α , α -dimethylethanol)-amino-2-methoxyacridine	Parke, Davis WIC-35	1050	14
9- α -hydroxy- γ -butenyl-9,10-dihydroacridine	Lilly AL-727	1071	17

their tumor growth.* In a number of instances mice bearing spontaneous mammary gland carcinoma remained in good condition with retarded tumors for more than 42 days when given food containing 0.1% brilliant orange 3R, Nyanza, C.I. No. 788.

Compounds that stained and retarded tumors resulted in atrophy of the thymus regardless of age, growth and general condition of the host. This action on the thymus resulted in loss of thymocytes. In every instance in which the tumor was stained the thymus was also stained. The factor that brought about atrophy of the thymus did not influence the behavior of other lymphoid tissue. The mesenteric lymph nodes, the pleural lymph nodes and those in the axilla and groin remained approximately normal in size even when stained by the compound.

Microscopic preparations showed the presence of many cells undergoing mitotic division in tumors in treated mice, even though the tumors in untreated mice increased in size more rapidly than those in treated ones. Tumors in untreated young adult mice about doubled in size every 36 to 48 hours; grafts grew into tumors 900 to 1000 c.mm. in 7 days and 8000 to 11,000 c.mm. in 15 days. Figures showing cells in prophase, metaphase and anaphase were abundant in preparations of retarded tumors; on the other hand few pyenotic nuclei occurred. From this it seems evident that multiplication took place slowly rather than that the drugs act as caryolytic poisons. In a few instances, where large enough quantities of compounds were available to prolong the treatment, the tumors continued to grow slowly and after

many days (30 to 40) they became moderately large tumors.

Discussion. Studies on malignant growths have established a general relationship between the well being of the host and rate of growth of malignant tissue. Agents that lower the growth rate of the host retard the growth of malignant tissue. In our experiments it was found that consumption of food containing toxic substances as well as lowered consumption of food resulted in retardation of the growth of both host and tumor. On the other hand retardation of tumor was not necessarily accompanied by ill health of the host. Some healthy, well grown mice had large tumors, others small tumors, depending upon the compound they received.

The retarding action of certain compounds, for instance A-79 and D-91, was so consistent that they were used to test whether the addition of vitamins, nucleic acids, coenzymes, surface active agents, etc., would increase or decrease the retardation of tumor growth in mice fed these compounds. Our results indicate that addition of nucleotides and thiamine to the diet in some measure counteracts the action of acridine compounds, but they are not as conclusive as those of McIlwain¹⁰ (1941) and Hegsted, McKibbin and Stare¹¹ (1945). McIlwain suggested that the nucleotides form complex salts with acriflavine components and that the dye might act in this manner to inactivate enzyme systems of which nucleotides are an essential part. He found that *B. coli* was inactivated by acriflavine, but could grow in the presence of acridine compounds with the addition of nucleotides which were not needed for growth of untreated bacteria.

* 2-methoxy-6-chloro-9-(3-methylamino-2-methyl-propylamino) acridine	Abbott	D-92
6-cyano-9-(3-ethylaminopropylamino)-2-methoxyacridine, hydrochloride	Abbott	D-94
9-(3'-diethylaminomethyl-4'-hydroxy-anilino)-6-chloro-2-methoxyacridine	Parke, Davis	WIC-1
9-(3'-n-butylethylamino-methyl-4'-hydroxyanilino)-2-methoxy-6-chloroacridine, 2HCl	Parke, Davis	WIC-22
9-aminoacridine hydrochloride	Sterling-Winthrop	WIN-146
2-methoxy-6-chloro-9-(4'-diisopropylaminobutylamino) acridine dihydrochloride	Lilly	A-66
9-(6'-allyl-3'-diethylaminomethyl-4'-hydroxyanilino)-6-chloro-2-methoxyacridine	Parke, Davis	WIC 2

Hegsted, McKibbin and Stare¹¹ found in studies on rats that the addition of atabrine to a thiamine deficient diet delays loss of weight, onset of symptoms, and death. Animals receiving low levels of thiamine along with atabrine showed greater weight gains than controls, so that atabrine seemed to have a "thiamine sparing" action.

Atrophy of the thymus occurs in mice due to age and to wasting diseases, but the loss of the cortical portion of the thymus in mice fed non-toxic, tumor retarding compounds was too constant to be attributed to the host's general condition. Van Herrswynghe²¹ (1934), who studied the action of tryptaflavin on the thymus and other lymphoid organs, claims that the manifestations presented by these tissues show that the thymocytes are different from lymphocytes. This view seems to be confirmed by our results. Atrophy of the thymus, however, cannot be attributed to the action of acridine compounds in particular since we found that it accompanied retarded tumor growth whether produced by acridine, rhodamine or oxazine dyes that stain tumor *in vivo*.

The influence of various compounds, particularly acriflavin, on mitosis has been studied by Dustin and Gregoire,⁷ 1934; Mayer,¹⁸ 1934; Dustin,⁶ 1939; Brock, Druckrey and Herken,⁴ 1939; and Ander-vont,² 1940. These investigators found that mitotic division could be interrupted in prophase and anaphase or stopped in metaphase by certain substances (tryptaflavin, sodium cacodylate, colchicine and others) which they termed caryolytic poisons. The investigations of caryolytic poisons in general showed that tumor cells are not influenced by all substances that effect other tissues. Colchicine produces a greater accumulation of mitotic figures in the thymus, germinal lymph centers, glands of Lieberkuehn, testicles and tumor. Tryptaflavin brought about only slight retardation of mitosis in tumor tissue while it caused intense reaction in the thymus. Dustin and Gregoire⁷ found that tumor cells show great sensitivity to agents that

excite mitosis (sodium cacodylate) and a great resistance to agents that retard mitosis (tryptaflavin).

A few of the acridine compounds have been used as therapeutic agents in studies on cancer by Lewin¹³ (1920); Marsh and Simpson¹⁶ (1926); Blumenthal³ (1931); and Lettré¹² (1941). Marsh and Simpson injected mice bearing spontaneous mammary gland carcinomata with acridine orange and with acriflavin intravenously and subcutaneously during an average period of 34 days. They found that the treatment had little therapeutic effect on tumor growth. Lettré reported that tryptaflavin inhibited complete mitosis and that daily injections of 0.025 and 0.05 mg. into mice implanted with an "ascites tumor" delayed the development of the tumor and prolonged the life of treated animals. Other investigators have reported that tryptaflavin does not effect mitosis of tumor cells. Ascites tumors, however, are formed by growth of malignant monocytes, not by fixed tissue cells (Farris and Yeakel,⁸ 1944.)

Lewin¹³ and also Blumenthal³ employed tryptaflavin and argoflavin intravenously in the therapy of human malignant tumors and reported that improvement followed for short periods of time. In our studies on mice it was found that while a number of acridine compounds had marked growth retarding action, none of them retarded an actively growing sarcoma or carcinoma sufficiently to have therapeutic value.

Structural Analysis. The acridine antimalarials were in solid, usually powder form, and the majority of them were hydrochloride or dihydrochloride salts. The solubility in water or some other solvent was known for many of the compounds. However, this failed to account for the power to stain or failure to stain tumor tissue which resulted from the administration of many of the 9-amino acridines.

Albert *et al.*¹ (1945) have demonstrated that highly basic acridines are almost completely ionized in solution to give cations, and that compounds which lack

amino groups have poor ionization and antibacterial activity. No data were available as to the ionization of the compounds tested for tumor staining. Therefore, we cannot determine whether adequate ionization is a prerequisite for staining, allowing other factors, such as side chain constitution and ring substituents, to become manifest. Indirect evidence, however, on the necessity of adequate ionization is the fact that all compounds lacking an amino group as a substituent of the ring failed to stain tumors. For diffuse staining of tumors, cationic ionization appears essential. When acidic groups were introduced into the side chains of the 9-amino compounds, the compounds did not stain.

In the group of the 2-methoxy-6-chloro-9-amino (substituted) acridines, from which the largest number of compounds were tested, it is difficult to decide from the structure of the 9-amino chain, the elements determining staining. Large additions to the molecule, as seen in 2-methoxy-6-chloro-9-[2-(2'-methoxy-6'-chloro acridylamino) ethylamino] acridine, interfered with coloration of tumor tissue. The majority of the hydroxy derivatives of 9-aminoacridine in which the hydroxyl groups were situated off of the alkyl-amino-alkyl chain did not stain tumor. Acranil, 3-chloro-7-methoxy-9-(2-hydroxy-3-diethylamino-propylamino) acridine, dihydrochloride, and Neo-acranil, 3-chloro-7-methoxy-9-(2-hydroxyethyl-amino-ethylamino) acridine, dihydrochloride, did give staining of tumors. Goetehius and Lawrence⁹ (1944) found these two compounds less effective as bactericidal and bacteriostatic agents than other amino-acridines. It was found by Browning and Cohen⁵ (1921) and Linnell and Stuekey¹⁵ (1940) that the hydroxy derivatives of acridine were inactive against bacteria. Only two compounds, in which the hydroxy-groups were substituents of the acridine structure, namely 6-chloro-9-amino-2-acridol, hydro-

chloride, and 2-hydroxy-6-chloro-9-(1'-methyl-4'-diethylaminobutylamino) acridine, dihydrochloride, were available for tests on tumors and they failed to stain tumors.

Certain substituted 9-amino acridines such as 9-(4-diethylamino-1-methyl butylamino) acridine which did not stain tumors or become concentrated in tissues did so if a 6-chloro, cyano, nitro or methyl group was present. Concentrations in tissues dependent upon the 6-chloro substituent are described in the analyses of Taggart²⁰ (1946) who found that 2-methoxy-6-chloro-9-(3-ethyl-amino-propylamino)acridine became concentrated to a greater extent in tissues than 6 other compounds analyzed by him. If retardation of tumor growth as well as staining are considered, it became evident that the majority of the 9-amino acridine compounds that stain tumor as well as retard it show dialkyl-amino-alkyl-amino chains in the 9-position. Increase in the size of the alkyl chain of the 9-amino derivatives with increase in the lipophilic properties of the compounds was no deterrent to staining of tumors.

Hata¹⁰ (1932) stated that the staining and penetrating properties of dyes of the proflavine and trypanflavine type were associated with 3,6-diamino groups. Proflavine, or 3,6-diamino acridine, on oral administration does not stain the host's tumor while Acridine orange, or 3,6-dimethylamino acridine stains tumors diffusely.

Further studies with various monoamino and diamino acridines may determine the structural requirements for staining.

Summary. In our investigations on the structural nature of compounds that stain and retard tumor growth in mice, 331 acridine compounds (26 non-amino, 270 monoamino and 35 diamino) were administered orally to tumor-bearing mice in known percentages of dry weight of their food.*

Two hundred and four of them stained

* A table has been prepared showing the structural formulae of the 331 acridine compounds studied, their source, percentage used, number of days fed, size of tumor and color at autopsy of the treated mice. The compounds are arranged as substituents of acridine based on the number of amino groups present on the acridine structure. Access may be had at the Wistar Institute to this table or to a microfilm of it.

tumor tissue (0 non-amino, 187 mono-amino and 17 diamino). The majority of compounds that colored tumors also brought about some retardation in their growth. The amount of retardation caused by 33 of the acridine compounds resulted in tumors that were 1/10 to 1/18 the size of those in untreated mice and 16 of them retarded tumor growth to such an extent that when the untreated mice died (14 to 16 days) with tumors measuring 8000 to 11,000 c.mm., the mice that had been fed these compounds were healthy and had tumors measuring 200 to 455 c.mm., or 1/20 to 1/40 that size.

The administration of acridine compounds did not prevent tumor growth or bring about regression of growing tumors. It simply slowed the rate of multiplication of tumor cells.

The majority of the 9-amino acridines that stain tumor tissue as well as retard its growth show dialkyl-amino-alkyl-amino chains in the 9-position. Analysis of the results from our studies on acridine dye-stuffs and antimalarials has shown the importance of the presence of amino groups as substituents of the acridine structure for staining.

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GOUT: REPORT OF AN UNUSUAL CASE IN A YOUNG MAN

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CONSIDERING the prevalence of gout and our ignorance of much of its etiology and pathogenesis, there are comparatively few articles on the subject in current literature. Neuwirth⁶ recalls that Daniel Sennert in the Sixteenth Century called gout the "physician's shame," *opprobrium medicorum*. The disease remains in that category, for there is still little we understand about this curious, crippling affliction.

Recently I attended a case of gout in which the bone and joint destruction were so far advanced that no parallel could be found in the literature examined. There were other aspects which were unusual enough to warrant a presentation of the case.

Report of Case. A. A., a 28 year old Filipino man, was admitted to the medical service at St. Francis Hospital, Honolulu, March 25, 1946. He was complaining bitterly of pain and swelling in his joints, particularly the distal interphalangeal joint of his left small finger. A few months previously his left hand had been caught in the drive-chain of a tractor. The pain had been slight until 4 days before admission at which time it became very severe. He had no complaints referable to other systems.

Past History. The patient is a Filipino born in San Fernando, Luzon, P. I. He recalled that before he was 11 years old he had recurrent bouts of pain in the metatarsophalangeal joint of both great toes. These continued at odd intervals through puberty and adolescence. Between these attacks he had neither pain nor limitation of motion. In 1939 he arrived in the Territory of Hawaii to work on a sugar plantation on the Island of Kauai. In May, 1940, because of pain and deformity in his right great toe, an operation⁷ was performed in the plantation hospital and the contents at the base of the second phalanx were removed. These proved to be sodium urate crystals.

Unfortunately the patient was not aware of the diagnosis of his ailment.

January 3, 1945, he was admitted for the first time as a private patient to St. Francis Hospital. His chief complaint was of pain in all the small joints of his extremities and in his spine. His oral temperature was 103.4° F. The positive clinical findings noted on the chart were confined to "swelling and pain of the small joints of the extremities." The ailment was diagnosed as chronic atrophic arthritis, and the patient was given supportive therapy plus sulfanilamide. He was discharged afebrile and free of pain on the 6th hospital day.

He was readmitted January 23, 1945 with swelling of his knees in addition to the previous complaints. This time his temperature was 102° F. He was put on the same regimen as before, and he was discharged on the 7th hospital day after the swelling and pain had disappeared. His diagnosis was rheumatoid arthritis and acute recurrent septic arthritis.

Family History. Non-contributory.

Dietary History. His diet had usually included milk, rice, vegetables, fruits, fish, and occasionally eggs or pork. Alcoholic beverages had rarely been taken before he left Luzon, and the amount he had had since his arrival in Hawaii was minimal.

Physical Examination. The patient was thin and undernourished; his face reflected anxiety and pain. His temperature was 101.4° F. All the positive findings were in the extremities. Most of the joints in the extremities were swollen, tender, and deformed; their movement was very restricted. Both hands deviated ulnar-ward. The distal interphalangeal joint of the right 5th finger was extremely tender, and purulent material (Table 2) was trickling from it. The right great toe was shorter than the left; and the scar from a previous operation was visible. Drainage of the infected finger was established and penicillin therapy instituted. A small "cyst" behind the right ear was opened, and the chalky material it contained proved to be sodium urate crystals. The Roentzen

ray photographs (Figs. 1 and 2) suggested gout, but because of the amount of destruction involved the diagnosis was not definitely ascertained until the crystalline material had been removed.

The patient was relieved of pain by colchicine. A purine-free diet, vitamins, and

whole-blood transfusions rounded out the medical regimen. After surgical consultation the tophaceous material was removed from the left great toe and a partial amputation of the toe was done. The same procedure was carried out on the finger that had been infected. Improvement followed. Ambula-



FIG. 1.—Roentgenogram of foot showing advanced destruction of bone and joint.



FIG. 2.—Roentgenogram of hand showing destruction of bone and joint with surrounding soft tissue swelling. Note punched out lesions in other digits.

tion was gradual, and the patient was discharged May 18, 1946 to the Maluhia Convalescent Home for further care.

Comments. This case has many aspects which contradict the traditional features of gout. It is rare indeed to see it in a young boy. Lansbury³ includes age of onset as a diagnostic aid and points out that the first attack seldom occurs before the age of 35. Yet this patient was able to describe vividly gouty symptoms which appeared before he was 11 years old. In the 100 cases analyzed by McCracken *et al.*⁵ the earliest onset was in a youth

The tophus which confirmed the diagnosis was unusually located. It is common to find them on the ear margins, but this one was found behind the right ear and had the appearance of a sebaceous cyst.

The finding of hyperuricemia is taken as indicative of gout in those individuals who have arthritis. This patient on 5 different occasions had blood uric acid determinations under the outside normal limit of 5 mg. per cent. Bauer and Klemperer¹ point out that the uric acid concentration does not reflect the severity of gouty arthritis. The suggestion that

TABLE 1.—NORMOURICEMIA AND BLOOD INDICES SHOWING INFLAMMATORY ELEMENT IN ACUTE GOUT

	Jan. 1945		Mar. 1946		Apr. 1946		May 1946	
	3	23	25		1	6	26	17
Blood uric acid, mg./100 cc.	3 3		3 0	4 0	3 6	3 7
Sedimentation rate, mm./60 min.	100		128	..	117	
Red blood cells, m./c.mm.	3 98	3 03	3 62		4 40
White blood cells/c.mm.	12,750	11,650	23,500		9900	7600	..	
Hemoglobin % (Sahli)	82.4	59.4	72 6	..	84.0
Differential blood count:								
Polymorphonuclears	93	90	91		72			
Lymphocytes	7	10	7		28			
Basophils	2					

aged 19. There are no reliable statistics available as to the incidence of gout among Filipinos. According to the patient, there was no one else in his community on Luzon that suffered from the same type of ailment. Checking the records of the Queen's Hospital during the past 10 years for gout in Filipinos, I found but 1 case; but since a total of only 74 cases had been admitted (and diagnosed), this incidence is without significance.*

Sydenham's⁸ classical description of gout appears to be the basis for the belief that this ailment is more prone to affect people who eat rich foods and imbibe freely of alcoholic beverages, though "poor man's gout" is also recognized. My patient had always been pathetically poor until he came to Hawaii. A basic food intake supplemented rarely by an alcoholic beverage composed his diet. Obviously diet had little influence on his contracting gout.

old cases of gout and gouty arthritis may have lower levels of blood uric acid than early cases was confirmed in this patient.

The roentgenograms (Figs. 1 and 2) of a hand and foot showed extensive bone and joint destruction. On this basis alone the involvement might well have been interpreted as due to a malignant neoplasm. This interpretation was at first suggested by a competent roentgenologist after he had examined only the Roentgen ray photograph of the foot; but the presence of the lesion in two extremities made the diagnosis of malignancy unlikely. There are numerous punched-out areas visible in the bones, but no roentgenologist could be expected to make an unequivocal diagnosis of gout from these pictures. McCracken *et al.*⁵ quote McClure and McCarty on this point and conclude with William's statement of a quarter of a century earlier that Roentgen ray is of little service in diagnosing gout, and it

* In June, 1945 the Territorial Board of Health statistics showed 47,863 Filipinos in the Territory of Hawaii.

may "lead one to arrive at wrong conclusions." Neuwirth⁶ emphasizes this same point.

Linton and Talbott⁴ show many interesting Roentgen ray photographs of cases which received surgical treatment. These exhibit more destruction than any others found in the available literature, and the results they obtained by careful removal of the tophaceous material is well demonstrated. Relief from crippling pain followed their surgical measures, and it was our desire to achieve the same goal in this case. This was accomplished with eventual rehabilitation of the patient.

It has not been sufficiently stressed in the literature that the acute arthritis due to gout is of an inflammatory nature. There is ample evidence to support this (Table 1). On each of the three admissions there was a moderate leukocytosis and a definite increase in the number of polymorphonuclear leukocytes. After the process had subsided, the leukocyte and the differential counts returned to normal. Although the sedimentation rate was over 100 mm. after 60 minutes when the patient was admitted in March 1946, it must be recalled that the patient did have a purulent infection in his finger. However, 1 month after admission the sedimentation rate was 117 mm., and there was no sign of pus at that time. This would suggest that the high sedimentation rate present at the time of admission was primarily due to the gouty arthritis. Further evidence was obtained by removing fluid from the left knee joint (Table 2). This fluid had a specific gravity of 1.023, with 250 polymorphonuclears per cu. mm.

TABLE 2.—EXAMINATION OF EXUDATES

	Culture from infected finger	Fluid from left knee
March 25.	Non-hemolytic Staph. aureus	Sp. gr. 1.023 250 cells (polys.) Culture—neg.
April 5:	Neg. for fungi	

In addition to the laboratory data, the temperature curve was above normal during all periods of pain. With colchicine and dietetic therapy the temperature (and

pulse) returned to normal in a few days. There were a few exacerbations during the hospital stay, but they were mild in comparison to the attack which brought the patient in for treatment.

Discussion. Though there is still no adequate knowledge of the etiology of gout, certain negative statements can be made: (1) It is well established that hyperuricemia is not the cause of gout. Fiessinger² clarifies this stand and discusses the etiology from the standpoint of heredity and allergy. If gout ever becomes more readily diagnosed by the clinician, it is probable that hereditary influence will assume a more important aspect in our study of the disease. (2) Eating rich foods, particularly those high in purine content, is no more the cause of gout than is eating a high starch diet the cause of diabetes. The disease process must be present in some degree; then the diet may precipitate clinical symptoms. It is not only gout's etiology concerning which we are ignorant. Colchicum and its alkaloid derivative colchicine, the drugs of choice for the therapy of acute phases, act in a way unknown to us. Yet colchicum was used for treatment of joint attacks as long ago as the Seventh Century.⁶

The importance of the clinician recognizing the diagnosis of gout as a possibility in any case of arthritis cannot be over-emphasized. That gout can mimic rheumatoid arthritis, polyarthritis due to rheumatic fever, acute osteoarthritis and acute arthritides due to bacterial infection should be obvious from the case history submitted. Since the prognosis and therapy for gout are widely divergent from other joint ailments, it is important for all physicians to consider gout seriously in their differential diagnosis of joint disease.

Summary. A case of gout is presented in which the following unusual features occurred:

1. The onset was previous to the patient's eleventh birthday.

2. The patient's diet was never very high in purines.

3. The roentgenograms displayed bone and joint destruction in excess of any found in the available literature.

4. Hyperuricemia was not present in several laboratory determinations.

5. A tophus was found behind the ear.

Criteria demonstrating the inflammatory nature of gouty arthritis are presented.

Physicians are reminded that gout can simulate other joint disease.

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THE PRINCIPLES OF VARIOLATION AS EXEMPLIFIED BY SUBCLINICAL IMMUNIZATION IN POLIOMYELITIS IN COOLER AND WARMER CLIMATES*

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REPORTS of groups of cases of poliomyelitis from tropical regions and from the Orient are likely to contain an excessive proportion of Europeans or Americans who not infrequently contract their disease while on even brief visits to these areas. This observation is remindful of the well-known epidemiologic principle that outsiders coming into endemic or seeded areas are, by reason of lack of immunity from previous exposure, more liable to attack than residents. But there is this important reversal: here the "outsiders" have come not from areas where the disease is less, but where it is *more* prevalent. Furthermore, the age of these patients is as a rule distinctly higher than that of native patients. An example is the report of Taylor on poliomyelitis occurring on the isthmus of Panama¹ from

1904 to 1942. In addition, even in the absence of reports of cases from tropical countries one is struck by the not infrequent development of the disease there in a visitor from this country. In conformity with many instances of this particular behavior of the disease, similar occurrences of poliomyelitis in British, American and Australian troops in the Middle East, Philippine Islands and in North China and Japan and in larger numbers (cited by Sabin²), has brought the phenomenon to the attention of a number of observers,^{3,4,5} made it the subject of extensive investigation, and as well, the basis of far-reaching generalizations concerning the epidemiology of the disease. The apparent immediate cause of the phenomenon is a higher level of immunity in natives (developing earlier in life as a result of more

* Immunization of the prepared host with active virus as distinguished from immunization with prepared (attenuated) virus, vaccination.⁶

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frequent exposure to the virus in individuals while probably still under the protection of maternal passive immunity). On the one hand the areas where the phenomenon has been observed include in general those with poorer sanitation. On the other hand reasons are seen for believing that poliomyelitis in temperate climates has changed "from a sporadic to an epidemic disease" in the last 50 or 60 years coincident roughly with improving sanitation, with a shift in age distribution to older ages. These considerations coupled with the presence of virus in intestinal discharges, so much emphasized in recent years, have led to the formulation by some of the tenet that "poliomyelitis is the price we pay for sanitation."^{48,49,60} In addition to its inference with respect to the mode of spread of the virus of poliomyelitis, this all implies that the disease in temperate climates in presanitation days behaved as it does now in the tropics. It also implies an exactness of correlation which does not seem probable between climate and improved sanitation extending all the way from Tasmania to Greenland. It further implies that climate *per se* is not a fundamental factor in the epidemiology of this disease.

Before deciding that man-made sanitation is responsible for such a difference in the behavior of the disease in warmer and cooler climates and has produced such a quick change from sporadic to epidemic occurrence in temperate climates, and before accepting these accompanying implications, it would be well to examine the record of the occurrence of the disease in point of time (also man-made), upon which the idea is based. Comparisons should be made with other diseases which exhibit the same behavior—and in which the various elements involved are more amenable to measurement. Finally it is necessary to seek in the information thus accumulated an explanation which might apply not to just one of its members, and with an element of doubt, but with more certainty to all of the group of diseases which exhibit the identical phenomenon.

Change From Sporadic to Epidemic? That a disease is "on the increase" has always been one of the most potent arguments in the launching of campaigns, but at the same time one of the most difficult of epidemiologic features to establish. There are many examples of apparent increases in disease which are clearly the result of the separation (frequently by the keen mind of a single observer) of clinical entities from larger classifications in which they had been included—or better, actually submerged. It would be difficult today, for example, to make any comparison between the actual incidence of appendicitis in the periods before and after Reginald Fitz. Again some advance in administrative, diagnostic, or therapeutic procedure may initiate or increase the recording of a disease not previously coming even within clinical recognition (*e. g.*, virus pneumonia and non-tuberculous pulmonary calcification).

The apparent increase in the occurrence of poliomyelitis in the last 20 years as compared with the preceding 20 year period is evidently attributable to increase in the recognition and reporting of non-paralytic (or preparalytic) poliomyelitis, which was raised to a new level in 1927.^{9a,37} There has been no such increase in the more stabilized reporting of deaths.¹¹

Indications of the occurrence of poliomyelitis can now be traced to the earliest times in the records and preserved remains of human history, but in medical literature it was not until the beginning of the 19th century that it began to emerge as a disease entity from the heterogeneous group of accepted but little noticed "crippled and deformed."¹⁶ It was through case descriptions of a particular kind of crippling which included some attempted association with one or another specific cause, that the concept of an epidemic infectious disease began to take form. Underwood's "Debility of the Lower Extremities" is generally regarded as the first of these: "Not a common disorder, attacking children seldom under 1, or

more than 4 or 5 years old, . . . in the instance of teething or of foul bowels."

At any rate, this and subsequent more definitive descriptions were forerunners of Heine's monograph in 1840, which, though dealing primarily with the orthopedic management of various paralyses, included the clinical course as well as his speculations on the etiology and pathology of the disease. He called it an affection of the "central nervous system, namely of the spinal cord, of an irritative and congestive sort"—good beginnings for present-day knowledge, but not until his concept had survived years of challenge by such theories as "essential infantile paralysis" did it lead to the next advance. Strümpell, in 1884, first suggested infection. In 1887, Medin observed the epidemic nature of the disease in Stockholm, and, in 1894, Caverly studied an outbreak in Vermont, added non-paralytic forms of the disease, and laid down the important epidemiologic features; and finally, the exhaustive studies of the 1905 epidemic in Sweden by Wickman carried the earlier work to the concept that the infectious agent was widespread largely through mild, abortive, or subclinical infections with the frank disease an exceptional outcome of the exposure to the infectious agent.

Taylor's epidemic⁵⁵ of 7 cases of paralytic poliomyelitis in the village of Cherryfield, Maine, in 1896, surpassed the great epidemic in New York City in 1916. Caverly's epidemic in Rutland County, Vermont,^{15a,b} which occurred 53 years ago was surely as epidemic in that population as any we have known later. To be sure, Caverly's epidemic extended only as far as he could travel with a horse and buggy, but numbers of cases which had occurred outside this area in the same outbreak became known later as well as cases which had occurred in earlier years. The earliest case in Vermont actually verified by examination by one author had occurred in 1852—almost back to Heine. Hirsch had to write in 1880 that "Historical inquiry . . . into the relations

of typhoid in time and place can only cover a somewhat short period with any exactness, a period counted by tens of years." If typhus abdominalis melts into an undifferentiated group so quickly when we try to trace it back, when we ourselves can remember many cases of poliomyelitis which had not yet been separated from "the crippled and deformed," it is no wonder that records of epidemics of poliomyelitis can be traced no further back than those of typhoid fever. One can judge—from the fact that even today many cases of poliomyelitis are the first in the experience of the physician, and many epidemics the first for the health officer of the community³² and Sinkler⁵¹ of Jacobi (Mary Putnam)³² and Sinkler⁵¹ in Philadelphia in the 70's, describing as they did all the types of cases seen today, certainly represented an experience with far more than a "sporadic" occurrence of the disease. Heine's monograph in 1840 indicates a familiarity with various types of cases equal to that of an orthopedic surgeon of today. Colmer's report of an epidemic of poliomyelitis 2 years later in the Parish of West Feliciana in Louisiana was a large epidemic for that population. And Underwood, in 1789, was not describing a rare experience in his description of "debility of the lower extremities" when he wrote that when 1 leg is affected the "above means (his therapy) in 2 instances out of 5 or 6, entirely removed the complaint; but when both have been paralytic, nothing has seemed to do any good but irons to the legs."

Van Riper fixes the change from sporadic to epidemic in various parts of the world with a precision which is believed to reflect the man-made record of poliomyelitis more than it does its actual occurrence in the past, when he writes, "Prior to 1870 poliomyelitis occurred only as a sporadic disease of the very young child. During the 1870's in Europe, the 1880's in Scandinavia, the 1890's in the northern part of the United States, and the 1930's in the southern part of the United States, poliomyelitis took on a new character—occur-

ring in epidemic proportions."⁶⁰ One of us remembers 2 individuals in his small home town in Georgia who had always been known only as "cripples" but who, after the occurrence of poliomyelitis in 1 of their children many years later, were both diagnosed as having had poliomyelitis in August, 1889—an attack rate in that small population equal to that of the New York City 1916 outbreak and coinciding in time with Medin in Sweden.

AGE DISTRIBUTION. The age distribution of "the immunizing infections of childhood" is a reflection of both opportunity for exposure and immunity existing at the time from previous exposure.¹² One determinant in the rapidity and extent of exposure to and development of immunity from exposure is density of population. Perhaps the most clear-cut example of this is the occurrence of measles at younger ages in urban populations than in rural populations in the same region. The disappearance to a large extent of the urban-rural difference in the age distribution of measles in many parts of the United States in more recent years has been attributed to the "urbanization" of what has been designated as rural populations. Such factors as increased facilities for transportation and consolidation of schools are generally considered as contributory.

Clinical observation alone has been sufficient to establish measles as one of the "immunizing infections of childhood" without benefit of either tests for detection of virus or of immunity resulting from infection. If only cases of measles with complications (middle ear, pneumonia, or post-measles encephalitis, for example) were recognized, that is if the rash had never been seen, the distribution of "measles" would only dimly reflect the dissemination of the virus and could not be fitted into any epidemiologic pattern in the absence of tests for virus or for immunity. The conception of the epidemiology of measles would be as vulnerable to challenge as has been the epidemiology of those diseases where in-

fection and the development of immunity is largely subclinical. Both Frost and Wenstedt many years ago interpreted the age distribution of poliomyelitis and especially the more rapid decline in cases with age in urban than in rural populations as likewise indicative of widespread subclinical immunity which accumulated more rapidly in urban than in rural populations. From a comparison of the age distributions of measles, diphtheria and poliomyelitis in urban and rural populations, it was concluded that the virus of poliomyelitis attained a distribution equal to that of measles and diphtheria and it was inferred that the mechanism of infection was the same for the 3 diseases, the essential epidemiologic difference being the frequency with which those exposed to the infectious agents developed clinical disease or subclinical infection. In measles there is a lack of evidence that subclinical infection occurs, but there is the possibility that exceptional individuals, giving no history of measles are presumably immune since they fail to develop the disease even upon repeated exposure. It may be that they were actively immunized through modified measles (unrecognized) resulting from exposure at a suitable time during the short period of their maternal passive immunity. In diphtheria subclinical infection is roughly 10 times that of clinical infection, and in poliomyelitis more than 100 times as great.¹⁶

In warmer climates even in less densely populated areas, the age distribution of certain of these diseases notwithstanding lower incidence indicates that dissemination of their infectious agents with resulting immunity takes place even more rapidly and extensively with reference to age than in cooler climates. Doull²¹ has shown that in diphtheria, scarlet fever and poliomyelitis there is a higher concentration of cases at younger ages in tropical and subtropical than in cold climates, a phenomenon interpreted by him as an indication of earlier and more widespread immunity in warmer climates. As he said, subclinical infection is regarded as being

more frequent in these climates than in colder latitudes where clinical forms are much more common.

Even within this country the same climatic difference can be discerned. It was noted, in 1929, that in spite of lower incidence of poliomyelitis in the South, the age distribution indicated "that immunization, as in diphtheria, is accomplished . . . with a rapidity equal to that in the North; this may in turn be regarded as evidence that the virus spreads to the same extent in the 2 parts of the country. It should be remarked that the close approximation between the age distribution in New York City and in the Southern States, the latter comprising a comparatively rural population, suggests that the virus may spread with even greater rapidity in the South from the point of view of age, and that the possibility of infection with the virus earlier in life in the South may be a factor in the production of the relatively more extensive subclinical immunization in the southern population. It should be stated, however, that there is no positive evidence that infection at earlier ages (*per se*) tends to produce subclinical immunity, excepting (by analogy with measles and diphtheria) possibly during the first few months of life, when there may be a temporary immunity derived from an immune mother which, if infection occurs during this short period, might bring about an active subclinical immunity."¹⁵

Thus, insofar as age distribution may be taken as a reflection of the rapidity and extent of virus dissemination, it would appear—from the fact the patterns are the same—that the mechanism of dissemination (and immunization) are the same in a group of diseases including diphtheria, scarlet fever and poliomyelitis, and that all 3 diseases exhibit the same evidence of earlier exposure in warmer than in cooler climates. The effect of an evident decrease in dissemination of the diphtheria bacillus (usually attributed to artificial immunization) in northern United States and Canada in recent years, on the age

distribution of diphtheria, has not been examined.

IMMUNITY. The epidemiologic inferences from studies of the age distribution of these diseases in respect to widespread dissemination and immunization (more largely subclinical, as so ably set forth by Wickman in his classic monograph on poliomyelitis) have been amply borne out chiefly by actual tests for immunity and in a more limited way by tests for detection of the infectious agents. Many Schick test surveys in urban populations have revealed immunity which increases with age to the degree which was fully to be expected from the decrease in incidence of the disease with age. The less rapid development of immunity and to a lower total level than that observed in urban populations has been determined by Schick test surveys in rural populations, notably the study of Kidder⁵⁶ in Vermont.

The results of extensive Schick test surveys in a number of tropical countries where clinical diphtheria is relatively uncommon have consistently shown higher proportions of immunes than are found in even more congested populations in northern areas.^{21,22b}

Tests for immunity to poliomyelitis, although carried out far less extensively than tests for immunity to diphtheria, have been done to a sufficient extent to indicate a similar population immunity. Neutralization tests on persons at different age groups in urban and rural populations revealed immunity corresponding closely with that to diphtheria as indicated by Schick tests.⁸² Numbers of tests in various parts of the world have indicated immunity in adults as extensive as immunity to diphtheria. Going to warmer climates, 20 of 21 adults in Atlanta, Georgia, possessed neutralizing antibodies.⁸⁵ Hudson and Litterer found the same in Nashville, Tennessee.³¹ A high proportion of sera from the Fiji Islands neutralized the virus.¹⁶ A similar high immunity has been found in adult natives of Liberia.^{20a,b} Immunity has also been shown in high proportion of small groups of adults in

China^{24,40} and in Puerto Rico.⁵² It is to be noted that the extent of immunity in adults in warmer climates, even though the population may be more sparse, is equal to or exceeds that of adults in more temperate climates. Doull, Hudson and Hahn²³ testing adults of the Philippine Islands found evidence of immunity to diphtheria, scarlet fever and poliomyelitis in a higher proportion of the sera than that usually found in temperate climates.

That the differences under discussion between cooler and warmer climates are not due to variation in sanitation with latitude but are in reality determined by climate itself is perhaps most strikingly suggested by the occurrence of the same differences in diphtheria between 2 cities in the same latitude—Santos and São Paulo, Brazil, not 50 miles apart but one situated at sea level and the other at 7500 feet altitude.^{22a} Altitude produces the same effect as latitude. The same difference has been observed in poliomyelitis in Bogota and at sea level in Venezuela.^{39b}

The parallelism between latitude and climate is, of course, not an exact one. In addition to altitude other factors such as ocean currents account for marked variations, as for example the effects of the Gulf Stream. On the North American Pacific Coast the more precise variations with latitude seen in the interior do not occur. A number of infectious diseases ordinarily conforming closely with latitude in respect to such features as incidence or seasonal prevalence are aberrant, partaking of some features characteristically southern and others characteristically northern. That the "climate" of the Pacific Coast possesses both northern and southern features is suggested by the fact that Timothy and Bermuda grass, respecting completely their northern and southern ranges elsewhere, overlap on the West Coast. In this connection it may be pointed out that poliomyelitis in Japan corresponds closely with poliomyelitis in the southern United States in respect to incidence, age distribution and seasonal prevalence.⁴⁵

Another related phenomenon common to this group of diseases is that of maternal passive immunity. Since in adults immunity is high, passive immunity in infants, as would be expected, is likewise high. This has long been established in diphtheria as lasting from 3 to 6 months by antitoxin measurement and has been demonstrated in poliomyelitis by virus neutralization tests.^{8c} The duration of maternal passive immunity in infants has not been so precisely established in poliomyelitis, but the close parallelism in the diminished incidence of the disease in infants under 6 months of age with diphtheria suggests that there is a similarly close correspondence in maternal immunity in respect to duration. This is borne out by the absence of immunity in a high proportion of children over 6 months but under 3 years of age (in temperate climates).

Just at the time when the results of immunity tests so generally accepted and widely used as a measure of the dissemination of other infectious agents were reaching the point of full verification of the implications of age distribution in respect to the pattern of infection with the virus of poliomyelitis, the epidemiologic significance of immunity in poliomyelitis was thrown into the shadow by the advancement of the theory that immunity was the result not of exposure to the virus but of "physiologic maturation." The idea that immunity, as shown by virus neutralization tests and even diphtheria antitoxin, was a spontaneous accompaniment of aging, was given considerable editorial emphasis under such headings as "Pan-immunity," "Automatic Environmental Vaccination," "Upsetting Immunologic Tenets," and "Phylogenetic Immunologic Recapitulation." Further doubts continue to be raised, doubts introduced through discrepancies^{17,12} in the neutralization tests but which are believed to be of the same order as less noticed discrepancies observed in immunity tests in other diseases. Such discrepancies led, as late as 1939, to the statement that "Polio-

myelitis antibody is not a result of exposure to or infection by the virus of epidemic poliomyelitis."¹³

In spite of all the questioning of the "epidemiologic specificity" of immunity, the immune reaction has never ceased to hold first place in the laboratory as a test for "etiologic specificity." The circumstances attending most of the "transmissions" of poliomyelitis to rodents are similar to those under which spontaneous but highly latent rodent virus diseases have been uncovered. Cross-immunity has been the main criterion for differentiation, as in the well-known examples of the 2 types—the Lansing strain of poliomyelitis and Theiller's virus. Whether the close biologic relationship between the infectious agents of 2 different diseases suggested by cross-immunity is an indication that both were derived from the same stem, whether one has arisen from the other by mutation, or whether their antigenic components only happen to have the same or a similar configuration, may be an interesting academic question but may not be of epidemic significance. There is evidence of cross-immunity between *T. pallidum* and *T. pertenuis* and "There has been much speculation on the possibility of syphilis having been derived from yaws or vice versa, but creditable evidence that this has ever occurred within historic times is lacking."¹⁹

Reëxamination of the question of transmission of poliomyelitis to rodents in the light of spontaneous rodent viruses which cross-immunize with poliomyelitis virus should go far to clarify some of the epidemiologic implications of "rodent poliomyelitis"—particularly those relating to extrahuman reservoirs in poliomyelitis. Furthermore, 1 of these immunologically related but etiologically unrelated rodent viruses, as suggested by Turner, in the case of *T. cuniculi* in syphilis or yaws, might (in the vaccine sense) actually constitute a vaccine against poliomyelitis.

It was not until Olitsky and Findlay's⁴⁴ neutralization tests—done in the face of the strikingly high incidence of poliomyeli-

tis in troops as compared with tropical natives and indicating high immunity in native children—that the implications of the earlier work on immunity again have entered heavily into conceptions relating to the epidemiology of poliomyelitis, and have finally attained a place in the minds of many as a true indication of widespread exposure to the virus—as widespread as is exposure in the other "immunizing infections of childhood."

Not only diminished incidence under 6 months of age but passive immunization in diphtheria and such procedures as convalescent serum protection against measles are all reasons for believing that maternal passive immunity is protective. Furthermore, such phenomena as production of modified measles and toxin antitoxin immunization and vaccination with immune serum-virus mixtures indicate that exposure to active virus under protection of maternal immunity or other protective influences may result in active immunization (subclinical).² Maternal immunity in offspring of immune mothers in a rodent poliomyelitis has been shown to protect against disease but to allow active immunity on injection of fully active virus. Virus injected early in the period of maternal immunity produced no effect; when injected later in the period of maternal immunity, the mice developed persisting active immunity (but without disease); when the virus injection was given still later, all succumbed to disease as was the case with the young of non-immune mothers when given active virus at any age.²⁰

In temperate climates, as shown by the several immunity tests and as reflected in the age distribution of disease, immunity of the population is at a high level during the first 6 months of life, at its lowest level at 1 to 2 years of age, after which it increases steadily and in accord with opportunity for exposure to the infectious agent until the high level which had existed at birth is reëstablished in adult life.

In tropical areas not only does the age

distribution of the disease suggest that exposure to virus more often approaches the early period of life when there is high maternal immunity but the neutralization tests of Olitsky and Findlay⁴⁴ in such an area suggests that the gap between maternal passive and acquired active immunity may be lacking. In 1946, they found that all of 72 sera from "healthy" natives of British West Africa from 1 to 40 years of age (8 were under 10) neutralized the MEF1 strain of virus. This strain of virus was isolated from a case in the Middle East Forces of the British Army and was shown to cross-immunize with the Lansing strain. Normal human serum possessed neutralizing antibody to the latter strain of the same order⁵⁹ of that repeatedly demonstrated against a number of monkey strains of virus.⁴⁴

A series of neutralization tests in 1933 and 1934, the interpretation of which was not entirely clear at the time,¹⁶ were done in the course of a survey of immunity to poliomyelitis in tropical island populations, one object of which was the finding (so far unsuccessful) of a population free of immunity, (needed at the time as a convincing answer to the challenge of spontaneous physiologic maturation). The possibilities of finding such an isolated population are not exhausted, but the occurrence of a "virgin soil" type of outbreak on the Island of Nauru, in 1910, restricted to the native half of the population suggests that a survey previous to that time doubtless would have uncovered an absence of immunity. The "isolation" of this group at that time is likewise suggested by the wide occurrence of leprosy in the same group following a clear history of its introduction a year later. Of sera from 32 natives of the Fiji tested against an American and an Australian virus, 26 of the 27 from adults showed the presence of antibodies. Sera of younger individuals, 11, 11, 12, 16 and 18 years old, all neutralized the virus, the 16 year old partial in 1 test but complete when retested. Of 27 sera from "normal" natives in Samoa, 23 completely neutralized and 4 gave evi-

dence of partial neutralization, the animals inoculated with the serum-virus mixture developing disease after incubation periods of 17, 18, 20 and 21 days, as compared with 7, 7, 8, 9 and 14 days in control animals. These 4 sera were from children 3, 4, 5 and 5 years of age. Nine other sera from children under 10 years of age completely neutralized the American laboratory strain of virus (isolated in Vermont in 1921). Though prolonged incubation periods had been suggested as representing partial immunity (in the serum under test),⁶⁶ this finding in respect to the sera of 4 children in the Samoan group was not considered sufficient to establish a difference from the usual immunity status of younger children in temperate climates (a relatively higher proportion of non-immunes). Subsequent observations have made it clear that prolonged incubation periods in such tests are indicative of the presence of antibody in serum.⁵⁰ In view of this and in the light of the results in the larger series of Olitsky and Findlay, these tests can be interpreted as indicating that the hiatus of immunity in younger children tends likewise to be filled in Samoa. The occurrence of partial neutralization suggests that active immunization was still in process of development at the time tests were done, a finding in keeping with the observation that active immunity can be initiated only in the later stages of maternal immunity when it is on the decline.²⁰

VIRUS DETECTION. That immunity as revealed by the several tests is a result of previous exposure to the infectious agent would no longer appear to need argument. Suffice it to say that wherever tested, either by clinical observation or by virus detection, the development of immunity has been in accord with opportunity for exposure. To be sure "control" areas (where virus and immunity are both absent) have not been found; but truly isolated populations insofar as human-to-human transmission is concerned are not to be found easily in the present day.

The last thoroughly studied "virgin soil" epidemic of measles (Faroe Islands) occurred just over 100 years ago. Perhaps the development of immunity to yellow fever, only in areas where there is opportunity for exposure and never in areas or in persons where previous exposure to the virus could be excluded, should suffice as "proof" of association between the presence of virus and of immunity.

In diphtheria Morales and Mandry⁴² have actually put to test the epidemiologic "hypothesis" that subclinical immunity is a result of exposure to the infectious agent in Puerto Rico. They followed a group of 194 native Schick positive school children with frequent throat cultures for diphtheria bacilli. At some time during the period of the study virulent bacilli were demonstrated in 26 individuals and in 168 they were never found. Of the 26 who harbored virulent organisms, 24 became Schick-negative and 151 (90%) of those who were never shown to harbor bacilli remained Schick-positive. Fewer data are available on scarlet fever, but wherever tested, to quote Doull, "every item cited in support of the explanation offered as to diphtheria holds true."²¹

As stated earlier, clinical observation alone affords a satisfactory demonstration of both the extent of spread of the virus of measles and of immunity resulting from infection with it. When immunity tests and virus detection are added, evidence is likewise afforded that the extent of dissemination of the subclinically immunizing viruses and of immunity from infection with them is of the same order as that in measles and, therefore, of an extent over the entire world only known to take place through person-to-person contact.

The disappearance of cholera in the United States within about 20 years after a widespread occurrence following its introduction in 1830 (described under the somewhat odd title "The Conquest of Cholera"¹⁷) soon followed when we began to get away from the river life of the times on the Mississippi and the Ohio. It well

illustrates the precarious method of transmission chosen by this disease. Cholera is now a problem only in restricted areas where optimal conditions for transmission exist. Typhoid fever has been able to maintain an existence only by reason of the added mechanism of chronic carriage. It too, however, is steadily diminishing, as with increase in sanitation the chances of continuous transmission are decreasing to the point where the failure of recruitment of new chronic carriers is causing it to lose its grip. Typhoid Mary is positively credited with only 50 odd cases in a lifetime, a feat which can be accomplished by a single case of measles in a day. Fecal transmission—an accident of hygiene—is not to be compared with the mode of transmission which has been described as ordinary, unavoidable, and the probable irreducible human contact, chosen by the upper respiratory infections, through which these infections enjoy a spread in the population to the point of saturation.

By the time the period of controversy which followed the challenge of "maturation" was subsiding, emphasis in epidemiologic research in poliomyelitis had shifted to attempts to establish the pattern of virus distribution through its actual detection. The "rediscovery" of virus in intestinal contents reopened the whole question of mode of spread of the disease with the result that exhaustive attempts were made to detect the virus not only from numbers of human sources but from a wide variety of non-human sources. There was a great emphasis on the detection of extrahuman virus reservoirs, which was doubtless prompted in part by the temporary dismissal of the large accumulation of evidence pointing to widespread subclinical infection and further stimulated by a resulting reemphasis of the long-known inability to demonstrate the criteria usually sought to establish contagiousness between clinical cases—the occurrence of disease in those associated with the sick. It became the fashion to "discard all previous conceptions"—the

force of the combined studies of Caverly, Wickman, Frost and Flexner—which had “dominated the scene too long” and to test any hypotheses by the sole method of virus detection; a phase of research which reached its height in a title as inclusive as “attempts to recover poliomyelitis virus from fruit, well water, chicken cords and dog stools.”⁵⁶ The confidence with which the hunt for extrahuman virus reservoirs was on is well illustrated by an abstract of the just mentioned article which seems to assume that failure to find the virus was only a failure in technique when it says: “Although the virus may have been present in the specimens tested, its existence could not be demonstrated when either the eastern cotton rat or the *Macaca mulatta* monkey was used as the test animal.”⁴³

During the period when immunity tests were largely relied upon as an indication of previous infection with the virus, relatively few attempts at actual detection of virus were undertaken. In view of the limited scope of researches which could be undertaken at the time, there was little chance in the first place of carrying out experiments on a sufficiently large scale. In the second place the end-point of virus infection as indicated by immunity tests rather than momentary harborage, as revealed by virus detection, seemed to be a better means of arriving at a conception of the actual extent of virus dissemination. During more recent years the detection of virus in intestinal contents has received far greater emphasis. Although it is clear that virus may be found in intestinal contents for a longer period than in the oropharynx where it has been detected during the 1st week of the infection (the period coinciding with the infectious period according to available evidence),^{7,96,14} it cannot be affirmed that it is more often present in intestinal contents. The large literature which has accumulated relating to the detection of virus in intestinal contents and in extrahuman sources will not be reviewed here, but it may be said that the results of such tests as well as renewed

detection of virus in upper respiratory passages^{29,35} have gone far to corroborate a virus distribution in the human such as would result, not from any extrahuman reservoir but from person-to-person contact as had been indicated previously both by studies of the age distribution of the disease and by the application of immunity tests. In this connection the work of Francis and his co-workers⁴⁷ and a recent study of Zintek⁶² on the dissemination of virus within a family, and of Howe and Bodian, who found virus in throats in juvenile family contacts and in throats of healthy children from a neighborhood playground,²⁸ may be cited.

It has been calculated that a diphtheria carrier rate of near 1% with an average duration of carriage of approximately 1 month^{26,61} is sufficient to account for immunity as indicated by the Schick test at any age group.^{8a} It was stated a number of years ago that “while no statistics are available concerning the healthy carrier rate in poliomyelitis, the virus has been detected in healthy persons. When we remember the relatively small number of attempts which have been made to detect the virus and the uncertainty of the technique by which this has been accomplished (it is not even readily transferred to the monkey from the spinal cord of known cases), the occasional reported finding of the virus in the upper respiratory passages of healthy persons might well be indicative of a healthy carrier rate not unlike that of diphtheria. When we consider, then, not only that the extent of immunity to poliomyelitis is the same as for measles and diphtheria, but that the rapidity of its development varies in the same way with concentration of population, we have evidence that both the extent and rapidity of the spread of the virus of poliomyelitis are the same as in measles or diphtheria.”^{1c} The more recent tests for detection of virus on a large scale such as those of Francis amply bear this out. It therefore may be said that the carrier rate in poliomyelitis (something

like that of diphtheria) would likewise account for immunity to this virus at different age groups of the same order as that of immunity to diphtheria.

Trask and Paul,^{46,57} who with their co-workers had used this method extensively, pointed out in connection with their detection of poliomyelitis virus in sewage and in intestinal contents, that the procedure used was in a number of ways highly selective for poliomyelitis as, for example, initial treatment of the inocula with ether on the one hand and the use of the monkey as test animal on the other. They actually "detected" tubercle bacillus in sewage as an incidental finding and stated that other "pathogenic bacteria, measles, mumps, etc., could have infected our monkeys without our knowing it." It is, then, not possible to attach proper epidemiologic significance to the presence of poliomyelitis virus in intestinal discharges in the absence of comparable information on other viruses. For example, is the virus of measles present in feces? As a matter of fact, lesions in the intestinal tract have been found in a number of diseases clearly not transmitted by intestinal discharges which make it likely that their viruses may also be present in intestinal contents and presumably in sewage. Koplik spots have been found in the colon in measles,¹⁹ as have been characteristic cellular changes in varicella.²³

In addition to such considerations as these, Paul and his co-workers have repeatedly called attention to the danger of basing epidemiologic inferences on this experimental finding alone: "But perhaps the most important question of all is, what does the finding of the virus mean insofar as the spread of poliomyelitis is concerned? In answer one could say that it is not evident from this work whether or not the presence of poliomyelitic virus in sewage is a direct or even an indirect link in the chain which usually or even occasionally leads this infectious agent from 1 patient to another in this disease. Our report merely calls attention to the

fact that during urban epidemics of the disease the local sewage may contain this virus."⁴⁶

Nonetheless this single laboratory finding seems to have been largely responsible for a very general shift from previously long-accepted conceptions to the belief that "the epidemiology of poliomyelitis may be considered to be similar to that of other enteric infections in which the causative virus is much more widely disseminated in the community during an epidemic than at other times."²⁴

It is this belief which forms the crucial link in the chain of argument that the lower incidence of poliomyelitis in warmer climates and its supposed increasing incidence in cooler climates is a matter of sanitation.

An ideal situation for studying the spread of disease would be afforded by an outbreak following the importation of a single case into an isolated and previously uninfected locality. But such an opportunity is seldom presented to the epidemiologist. Under actual conditions it is practically impossible to determine whether a given case is the first occurrence of the disease, or to group those cases which are related. Multiple cases in families present perhaps the nearest approach to epidemiologically connected cases.³ Chapin,¹⁸ Hill²⁷ and Frost,^{25,38} all chose familial aggregation for studies relating to the manner and the extent of dissemination of such diseases as measles, diphtheria, scarlet fever and poliomyelitis. The results of all the studies reviewed in this paper amount to hardly more than a geographic extension of the combined findings of these 3 great epidemiologists. Their studies supported the view that the "tendency to run through a family" was the same with all these infectious agents, and that the differences in familial aggregation of cases are due to differences in the frequency with which clinical or sub-clinical infection is the result of exposure.

Since the patterns of virus dissemination and immunity are essentially the same in the members of this group of diseases.

poliomyelitis, diphtheria and scarlet fever, it is believed that the relative frequency with which clinical disease and subclinical immunity results from infection with the different infectious agents cannot be accounted for in general by "immunity from previous exposure" but are actually due to different autarceologic factors in the different diseases. The question has been little studied in diphtheria and scarlet fever. In poliomyelitis there are a number of selectivities seen in the occurrence of the frank disease in the few of the many exposed to the virus which indicate that this "complication" of the ordinarily subclinical infection is determined primarily not by circumstances of exposure to the virus but by autarceologic influences. The notable example—already being taken into account in the prevention of numbers of cases of a particularly distressing and highly fatal form of the disease—is bulbar poliomyelitis following tonsillectomy and adenoidectomy.

Though the frequency with which the different infections are clinical or subclinical may be highly individualized in general, as the result of the operation of different autarceologic factors in the separate disease, they all possess a corresponding reduction in the frequency of clinical disease as compared with subclinical infection as warmer climates are approached. The evidence for a similarly more rapid and extensive dissemination of all the infectious agents in warmer climates suggests that earlier infection in warmer climates and hence more often under the protection of maternal passive immunity may afford the explanation for this phenomenon which the 3 diseases have in common.

MECHANISM OF INCREASED VIRUS DISSEMINATION IN WARMER CLIMATES. A mechanism which may account for the dissemination of virus at a more rapid rate and more extensively in the tropics is suggested by a study of amplitudes of seasonal variation in a number of diseases in cooler and warmer climates.^{5,10} In respect to amplitudes of seasonal variation

the curves of seasonal prevalence of a number of diseases in cooler and warmer climates all fit closely one of 3 curves. With certain exceptions bacterial diseases which spread directly from person to person have an amplitude of low order. Another group including diseases transmitted by intermediary hosts have an amplitude of higher order; and a third group, virus diseases, exhibit a still greater amplitude in seasonal variation. It was considered significant that the 3 curves in respect to amplitude occur in exact multiples. The reason for the exact multiple relationship was believed to be the simultaneous influence of season on 1, 2 or 3 factors involved in the occurrence of diseases of the respective types. It was suggested that 1 of the factors involved in the group of diseases exhibiting an amplitude of a higher order was, in addition to seasonal variation in susceptibility to disease upon exposure, a seasonal variation of the same period and phase in multiplication and hence in spread of the virus. For example, under this conception it could be reasoned that the virus of poliomyelitis requires host conditions of warm weather (or warm climate) both for disease production and for multiplication and hence propagation. Such a conception under which this virus could be active for only a brief part of the year in more temperate climates and throughout the year in warmer climates, could account for the more rapid and extensive dissemination of the virus in warmer climates.

Thus the reason for one of the puzzling paradoxes of poliomyelitis—the fact that it is a disease of warm weather but of cool climates—finally begins to come to the surface. For many years it has been evident that the conventional explanation for seasonal prevalence of disease—a corresponding variation in the mechanism of transmission—could hardly account for the seasonal prevalence of poliomyelitis in the face of this feature of the disease.¹⁵ Nonetheless, adhering to the old doctrine that contact diseases are diseases of winter

because of crowding, the seasonal prevalence of poliomyelitis has always been the point of departure for opposed hypotheses.

Under the same doctrine the view originating largely in carrier studies during World War I, that an increased carrier rate is always the forerunner of an increase in meningococcus meningitis, in spite of many discrepancies in the evidence, had come to be generally accepted. During World War II an extensive meningococcus carrier survey was conducted over a period of 4 years by Dr. J. H. Mueller under the Board for the Investigation of Influenza and Other Epidemic Diseases, Office of the Surgeon-General, United States Army. An analysis of the carrier rates, especially Type I meningococcus, the type found to be the cause of practically all cases, revealed no seasonal variation in carriage which could be associated with seasonal variation in the disease. As a matter of fact, carrier rates in summer were as high as in winter when the disease prevailed. This observation points to variation in frequency of clinical disease in carriers rather than to any variation in transmission of the meningococcus as the determining factor in the seasonal prevalence of meningitis, and suggests seasonal "predisposing" factors as the major determinant of meningitis in meningococcus carriers.^{4,5} Little information is available on the year-around prevalence of other infectious agents. But if the findings of the virus of poliomyelitis in sewage only in the poliomyelitis season^{41,57} or a prevalence of carriage in summer as suggested by the seasonal prevalence of bulbar poliomyelitis following tonsillectomy¹² can be compared with the seasonal prevalence of meningococcus carriage based on some 50,000 throat cultures, there is the suggestion that the meningococcus is capable of multiplication and propagation the year around, while multiplication of the virus of poliomyelitis is restricted in respect to season. This suggests that seasonal (or climatic) changes influence the suitability of the human host as a "medium" for the growth of the virus. This view is consistent with the fact that

meningitis exhibits an amplitude in seasonal variation of a low order, and poliomyelitis one of high amplitude in temperate climates and lower amplitude in warmer climates.

A review of the observations which form the basis of this paper serves to lend strength to the view that the spread of the virus of poliomyelitis is extensive and, as has been stated, a function of ordinary, unavoidable and irreducible contact. It furthermore emphasizes that infection with this virus is preponderantly benign—the one serious sequel of infection, paralysis, occurring in only a small fraction of those exposed. In the tropics the evidence indicates that in terms of parasitism adaptation between virus and host is even more nearly balanced. Widespread exposure to the virus, more frequently during the persistence of equally widespread maternal immunity, apparently results in more frequent modified infection (but still with propagation of virus) with resultant active immunity to be passed on to the offspring for repetition of the cycle. Thus we can say that we have achieved a high degree of commensalism with the virus (or the virus can say that it has achieved a high degree of commensalism with us).

Immunization (as in smallpox) would appear to be the approach to control of an infection as widespread as is poliomyelitis. The feasibility of vaccination against smallpox (carrying with it a certain hazard as would be expected in any prospective procedure in poliomyelitis) lies in part in the fact that the protection of the individual far outweighs the hazard of the vaccine. Vaccination at the same time removes its subjects from the reservoir of potential "carriers" of the virus which in former days was sufficient to make this disease one of the group of widespread immunizing infections of childhood. It may be doubted that this reason alone (if vaccination were of small benefit to the individual) would constitute a sufficient argument for the procedure. Pasteur's vaccination against rabies in the human is rendered feasible only by

reason of the circumstance that its administration can be restricted to the few in whom there is a high risk of rabies—those bitten by a rabid, or suspected rabid animal. The hazard of the vaccine in the population in general (postvaccination paralysis alone) would, numerically at least, far exceed the risk of the disease.

In respect to the employment of the principle of vaccination in poliomyelitis numerical considerations more like those of rabies than those in smallpox obtain. While a vaccination procedure might, as in smallpox, diminish the "virus reservoir" (conversion of non-immune individuals capable of multiplying and transmitting the virus to immunes not capable of doing so), if any prospective vaccine carried a hazard approaching the "natural" risk of disease in the individual, its applicability would be highly doubtful. Indeed, we have been through 1 experience where the risk of attempted immunization proved to be about as great as the risk of disease.^{39a} If, as in the sense of selective immunization in rabies, the use of a poliomyelitis vaccination could be restricted to the few who are susceptible to *paralysis in poliomyelitis*, vaccination in poliomyelitis would be quite a different matter.

If this concept offers an explanation of one of the long puzzling paradoxes of the disease—a disease of warm weather but of cool climates—it at the same time introduces another—that the disease is one of cooler climates where the dissemination of the virus is less and not of warmer climates where it is more. This might seem almost to constitute an argument (seeing that the virus is preponderantly immunizing rather than paralyzing—and even more in warm climates and by reason of earlier exposure) that speeding-up the spread of virus rather than hampering it (isolation, quarantine, etc.) would be a more effective preventive measure against paralysis than any that

we have. At any rate, harking back to Gorrie's attempt to prevent malaria (developing in hot weather) by chilling a room,* it does suggest that the principle of variolation (immunizing the young by inoculation of active virus in a hot room, as it were) should be explored as well as that of vaccination (attempts at further attenuation of the naturally highly "attenuated" virus) in the search for a better way of adding to the already relatively high protection against paralysis in natural infection with the virus.

Conclusions. Evidence derived from the age distribution of the recognized disease, from immunity as shown by the neutralization test and from actual virus detection indicates that the rapidity and extent of dissemination of the virus of poliomyelitis is the same as in the other "immunizing infections of childhood."

In respect to incidence of frank disease, age distribution, rapidity of development of immunity and extent of immunity, poliomyelitis exhibits the same differences between cooler and warmer climates as other "immunizing infections of childhood" in which subclinical immunization occurs.

The reason for relatively lower incidence of frank disease and higher subclinical immunization in warmer climates would appear to be the same in the group of subclinical immunizing infections of childhood and to lie in earlier exposure in warmer climates—at younger age when maternal passive immunity is still present in sufficient degree to protect against frank disease but to allow "modified" infection with resultant active immunity. The reason for earlier exposure in warmer climates would appear to lie in climatic and seasonal variation in the human host as a suitable "reservoir" for multiplication of the virus. There are indications that host-virus activity may tend to be seasonal in temperate climates and year-around in warmer climates.

* John Gorrie, a student of climate and fevers in Apalachicola, Florida, by way of perfecting his "technique" of fever prevention and cure, invented the gas compression process of refrigeration. There is no record that his treatment for malaria was successful—nor his invention—for him; but he is the father of air-conditioning, and all its application to health. Marshall Taylor's story of Gorrie (President's Address, Southern Medical Association in 1935⁴⁰) is fascinating reading.

Studies relating to the control of infectious disease, the ultimate goal of which has been eradication, have long centered on the infectious agent and its mode of spread, not only as a *sine qua non* but as the *ne plus ultra* for prevention. The studies relating to subclinical immunization reviewed in this paper suggest that

in poliomyelitis all the other elements entering into what constitutes an extraordinarily high degree of balance between this parasite and its host should be taken into consideration in attempts to prevent the one serious and exceptional sequel of infection with this virus—paralysis.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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THE STRATEGIC AND TACTICAL INFLUENCE OF DISEASE IN WORLD WAR II

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THE memory of men going ashore on a Normandy beach or approaching a Pacific island—American soldiers going into action—is still too vivid to leave any doubt as to where wars are finally won or lost. As certain as that may be, modern warfare is such that influences other than the courage of the men concerned or the quality of their leadership in combat, act strongly in determining the result. Disease and injury, and the quality and kind of medical care, constitute 1 such factor.

No attempt is made here to determine the relative importance of medicine and the other necessary services supplied to combat forces. It is likewise left to others—to the professional soldier, the statesman or the historian—to state the place of medical matters among activities that involve the whole of a population at war; the production of war materials, the management of economic stresses, and the maintenance of that fine balance of political and social interests within a nation and in respect to its allies. Few medical officers would attempt either evaluation; certainly not a civilian physician-soldier whose service was limited to the army in the field. The present analysis is confined to some of the ways that medical affairs enter into the management

of military operations and the extent to which they influence the result. Since the experience and the data are wholly of army origin, the consideration of strategic and tactical influences of disease will relate only to that part of military activities. Most of the examples cited are from the European Theater of Operations of World War II.

RESPONSIBILITY FOR HEALTH. That the maintenance of the health of troops is a function of command is an accepted part of military theory⁴ and so prescribed in the regulations of the United States Army.^{26a} Time was when this meant principally an adequate attention to the care of the sick and wounded. The past half century has brought about a greatly broadened interpretation of this obligation, to the extent that the prevention of disease now ranks as a coördinate activity.

While modern military medical practice has 2 principal objectives, those of medical care and preventive medicine, the organization for provision of these services is by no means to be interpreted as consisting of 2 parts. These primary interests overlap, and the successful accomplishment of both objectives depends upon the extent to which they are integrated into a single practice, which recognizes no

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sharp distinction between what is preventive and what is curative medicine.

Medical care in military practice has come to involve much more than the simple issue of death or recovery. Increasing attention is directed to the development of improved method for the prevention of physical defect after disease or injury, and for limitation of the period of disability.²⁵ Both features act toward the welfare of the individual, and from the viewpoint of military operations are important considerations as they affect available and effective manpower. They represent medical care directed toward preventive ends.

Preventive medicine has likewise developed far beyond its original interest in the control of the communicable diseases and a concern of environmental sanitation. The prevention of disease in general, whether it be communicable or non-communicable, is now an established part of the program for prevention,²¹ together with an interest in the limitation of traumatic and other injuries. In military practice, clinical and preventive medicine have become so nearly equal in emphasis that medical influences in military operations might be approached equally well from a consideration of the strategic and tactical influence of health, as from the standpoint of disease.

ADMINISTRATIVE MECHANISMS IN MILITARY MEDICINE. Since the responsibility for health is a function of command, it follows logically that need exists for a command adequately informed of health activities and health methods. The medical officer and the other technical experts of the Medical Department charged with health matters through delegated responsibility, have equal need for an appreciation and understanding of military matters. The failure of a commander to understand and evaluate medical risks can be just as costly as to misjudge the fire power of the enemy. A lack of understanding on the part of the physician of that fine balance between military necessity and medical losses can be similarly inhibitive of the

common effort which is the successful prosecution of a campaign. No remote suggestion is advanced in discount of the idealism that characterizes the practice of medicine; that is one of the finest parts of the profession, but war is not an idealistic business. It becomes necessary at times to look upon the health problems of a command from the standpoint of the group, to accept minor losses in order to effect major gains, and to weigh cost against military objective. The physician in military practice soon comes to appreciate that much of what he hopes to accomplish depends upon the support, the understanding and the aid that comes from his commanding officer. The medical officer must be equally cognizant of the objectives and requirements of command, for the measure of common accomplishment is generally determined by how well they understand each other.

These considerations are introduced because they are believed fundamental to an understanding of the influences that disease exerts on the conduct of war in the field, and to proper interpretation of the health record that results. This being the primary purpose of this presentation, rather than the methods and organization involved, a brief consideration of the 3 lines of approach to the management of health matters will suffice.

Command is called upon for a good deal more than intelligent understanding and direction of health activities. There is need for active participation. The good commanding officer gives interest and attention to the clothing, equipment and general well-being of his men, as well as to the adequacy of their training and the state of their military bearing. General Patton was the soldier, his primary concern with strategic and tactical matters. Perhaps that was the reason for his interest in the program of nutrition sponsored by the Medical Department, namely, that it fitted so logically into the framework of his strategic and tactical interests.

The direct responsibility for provision of medical care to the sick and wounded

falls wholly upon the Medical Department. The elaborate provision for casualties in the forward areas during the war just past has been thoroughly and adequately described,²⁷ from battalion aid stations, to collecting and clearing stations and to definitive care of non-transportable cases in field hospitals, or in sections of field hospitals to which auxiliary surgical teams were attached. The chain of evacuation extended to evacuation hospitals and back through the lines of communication to the great general hospitals.²⁸ Station hospitals cared for the needs of troops of the Communications Zone and of those of rest and reserve areas; and back of all were the major facilities of the Zone of the Interior for those seriously incapacitated or with disabilities of long duration.

A fundamental difference between the services directed toward medical care and those of preventive medicine is that successful accomplishment of the latter depends to a far greater extent on a coöperative effort of all arms and services. The supervision and control of preventive activities is, to be sure, a function of the Medical Department and much of the technical service is provided by that part of the army; the inspection and control of food supplies of animal origin by the Veterinary Corps; and the laboratory services so essential to the modern program of prevention. The unit surgeon is the health officer of his organization and he is aided by the special divisions of preventive medicine which are a part of all major commands. These strictly medical activities are however only a part of the comprehensive program for prevention. The Corps of Engineers has responsibility for the provision of potable water, the disposal of sewage and refuse and other activities which enter into the program for environmental sanitation. The food program of the army brings into play a close coöperation of Medical Department and Quartermaster Corps. The Medical Department is charged with the adequacy of the ration, the Quartermaster Corps

provides it to troops and assures its quality. The design and provision of satisfactory clothing and equipment are other responsibilities of the Quartermaster which relate strongly to matters of health. The provost Marshal finds direct participation in health activities by way of the program for control of venereal disease, and the prevention of accidents. The Chaplain also has a concern with venereal disease control, and a still broader interest through matters of psychologic and moral well-being which enter so largely into the health of an army. The Special Services Corps was a principal agent in public health education. In summary, preventive medicine in the army as in civilian practice depends for its success upon a community effort. It succeeds in its objectives to the extent that the various arms and services are brought into a common program.

CLASSES OF MILITARY CASUALTIES. Military casualties are divided into 3 categories, those of battle casualties, non-battle injuries and those the result of disease. Disease is thus set apart from injury as a source of disability, with a further distinction of injury as it relates to battle or non-combat origin. The separation of the many conditions involved is generally clear-cut, but for some the decision is made arbitrarily. Trench foot contracted by soldiers in the line is classed as a non-battle injury, although reasons of lesser moment have been advanced in claim of combat status. It is likewise evident that similar events are classified differently according to the circumstances under which injury took place. A gunshot wound of the hand incurred accidentally in a training area, or contracted anywhere as a self-inflicted wound, is a non-battle injury, and distinct from the battle casualty that results through contact with the enemy. The definition of terms that follow is from Army Regulations.^{26b}

Patients are classified according to the primary cause of initial admission and re-

ported in 1 of 3 categories of cases: disease, injury, or battle casualty. In instances of patients suffering from both disease and injury at the time of initial admission, the most serious condition present is taken as the primary cause of initial admission and determines the classification. Patients admitted for a battle casualty and a disease or injury are classed as a battle casualty.

All cases other than those due to injury or battle casualty are classed as "disease." Included among the disease cases are patients suffering from reactions to medication other than acute poisoning, patients admitted for the sequela of an injury incurred prior to entering service, and patients readmitted for the results of a traumatism (battle or non-battle) incurred during service.

The term "injury" includes traumatisms other than those defined as "battle casualty." The term "traumatism" refers to morbid conditions due to external causes. It includes acute poisoning, except food poisoning, the results of exposure to heat, cold and light as well as various types of wounds.

A battle casualty is a traumatism (wound or injury) which is incurred as a direct result of enemy action during combat or otherwise, or is sustained while immediately engaged in, going to, or returning from a combat mission. It does not include traumatisms occurring on purely training flights or missions. Psychiatric cases occurring in combat are not reported as battle casualties.

The measurement of losses from whatever cause is accomplished by computation of rates that relate to 3 principal demographic characteristics. The first of these, mortality, is the expression of the number of deaths from a particular cause that occur per unit of population and time, the ordinary unit of population being 1000 men and the interval of time 1 year. The rates for shorter periods are based on the assumption that the observed frequency would have continued over a year. The mortality rate represents a definite and certain military loss, irrespective of cause, of time or of nature, and is one of the absolute indices of the cost of war.

The morbidity rate expresses the num-

ber of persons affected by a given condition as determined by patients admitted to hospital or quarters, in relation to the same units of population and time as serve for mortality. Morbidity rates as so defined do not represent all persons affected but only those seriously enough involved to be absent from duty. Nevertheless, these indices of illness as employed in military practice are more satisfactorily indicative of the existing situation than is usual in public health or preventive medicine, because reporting is particularly good. The interpretation of the significance of any particular morbidity rate as an influence on tactical and strategical operations depends, in the first instance, on the duration of the disability ordinarily associated with the condition; secondly, on the expected fatality; and finally on the probability for complete recovery and return to duty.

The commander of a military organization ordinarily finds the daily non-effective rate the most valuable single index of the health of troops. As the term indicates, this is representative of the number of men absent from duty by reason of disease or injury for each 1000 troop strength per day. The complementary value shows the proportion available for duty at any prescribed time.

NON-EFFECTIVENESS IN THE EUROPEAN THEATER. Experience of the European Theater of Operations in respect to non-effectiveness of troops by reason of medical disability is shown in Figure 1. It is to be noted here that these data and all others included in this study are from field records and therefore subject to revision and correction when the final analysis of individual case records is eventually completed. The provisional data are believed sufficiently reliable to establish relationships and trends. Some are from theater sources; a great part were made available by the Division of Medical Records, Office of The Surgeon-General, United States Army.

Discounting the early part of 1942 when the small troop strength accounted

for irregularities in the demonstrated pattern, each year of the 4 year period of World War II saw the high point of non-effectiveness centered about the early months of the calendar year and minimal values during the summer.⁸ The seasonal incidence of upper respiratory infections was the dominating influence. Variations from year to year were not great

involved. The non-effectiveness related to disease continued according to established pattern, with rates in 1945 almost identical with those that characterized 1944, the year just preceding the campaign. A significant part of the excess non-effectiveness came about through a greater frequency of non-battle injuries, principally trench foot. The most impor-

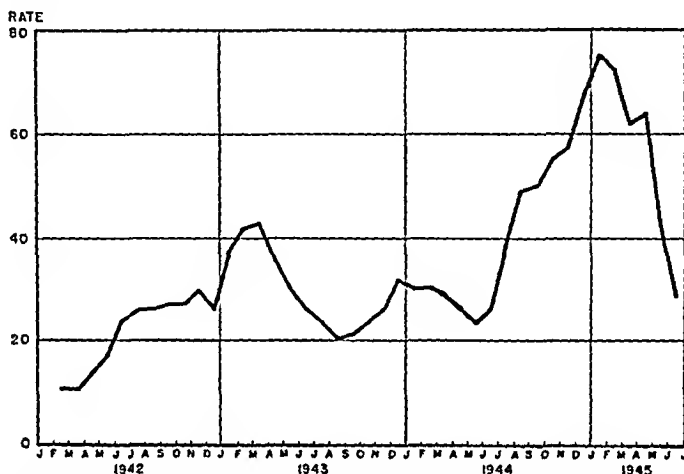


FIG. 1.—Average daily non-effective rates per 1000 strength, European Theater of Operations, U. S. Army, by months, February 1942 to June 1945 inclusive.

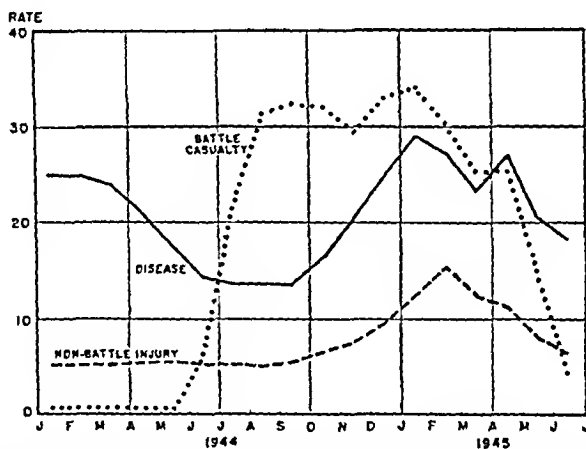


FIG. 2.—Average daily non-effective rates per 1000 strength, disease, non-battle injury and battle casualty, European Theater of Operations, U. S. Army, January 1944 to June 1945 inclusive.

until the latter part of 1944 when the values for all months increased precipitately over the established norm. This was coincident with the beginning of active operations in Continental Europe.

The division of this particular experience into the 3 components which make up the total non-effective rate (Fig. 2) gives ready demonstration of the factors

involved. The data of Figure 2 demonstrating clearly that the high non-effectiveness of the campaign period was due to that cause.

The generalizations to be drawn from this experience are that year in and year out the principal cause of non-effectiveness of troops is disease. The losses from non-battle injuries are ordinarily much

less, about one-fifth those from disease. The non-effectiveness that comes from battle casualties is subject to great variation and is wholly related to the nature of operations. The impression is not to be left that the cost in battle casualties is unpredictable, for the expected losses in a major operation can be computed with an exactness rivalling that of disease and injury.

It is noteworthy that the rates for all 3 classes of casualties are susceptible to irregular fluctuations which can be related with much certainty to environmental, seasonal, or other ecologic factors.

The peaks of excess incidence that mark the behavior of battle casualties and non-battle injuries are as outstanding as any introduced into the curve for disease through action of an epidemic in the common definition of the term.

DISEASE AS A FACTOR IN MILITARY OPERATIONS. That disease as a cause of death and disability has become a matter of far less significance in the wars of the past half-century is a matter of general knowledge.⁹ It is not so generally appreciated that the changes that have occurred are qualitative as well as quantitative.

The ratio of deaths from disease to deaths from battle casualties* for the wars of the 18th and 19th centuries was sometimes as great as 13 to 1. A generally accepted ratio was 4 to 1, as for example, in the Turko-Russian War of 1877-78¹⁰ where deaths from disease numbered approximately 80,000 and those from battle casualties 20,000. The ratio during the campaign in the Crimea was even greater, with some 70,000 deaths from disease and 7500 from battle casualties among the French forces. Essentially two-thirds of the deaths that occurred in the Union Army during the American Civil War¹¹ were from disease, which marked an improvement over the Mexican War of 1846-47 when deaths from disease outnumbered those from battle casualties 7 to 1.¹² The record during the Spanish-

American War¹³ was less satisfactory, with an excess of deaths from disease over losses in battle in the proportion of about 13 to 1.

Fewer deaths from disease than from battle casualties were noted for the first time (Table 1) in the War of 1864 which Denmark waged against Austria and Prussia.¹¹ Both opponents established a ratio of 1 death from disease to 2 for casualties of battle.¹² The number of men engaged in that war was small, communications between the armies and home countries were good and environmental conditions were favorable; and yet this was a remarkable event, a turning point in the history of wars. The Franco-Prussian War of 1870-71 was the first major war⁹ to see the new ratio maintained, by the German Army with a proportion of 0.86 deaths from disease for each battle casualty. The health record of the German Army has indeed been consistently good, for of 5 wars, dating from the Danish action of 1864 and including World War II, deaths from disease have been less than those from battle casualties with the single exception of the War of 1866 and that was close to parity. The Russo-Japanese War of 1904, the next great conflict after the Franco-Prussian War, gave the Japanese forces an opportunity to set a new record²⁰ of 0.37 deaths from disease per battle casualty. World War I was the first American experience in which a similar result was attained, providing troops in the active European campaign of 1918¹⁸ be considered (Fig. 6). For the army as a whole and representative of all men under arms the ratio was still in favor of disease (Table 1). World War II brought a complete departure from previous experience, and a health record never approached previously in any war.

The gains which have been made in recent times in the cost of disease are primarily due to improved control of acute infectious processes. Not only are deaths far less frequent in proportion to those at risk, but the incidence of communicable

* Grateful acknowledgement is made to Lt. Col. Irvine H. Marshall, Medical Corps, United States Army, for the data of Table 1 upon which this discussion is based.

disease is decidedly less. This has brought significant changes in the qualitative character of the losses that still result from disease as distinguished from injury and battle casualties. Non-communicable disease has become a far more significant consideration. That the frequency of this class of disability had a direct relationship to military operations is illustrated by the data of Figure 3.

During the time that active combat operations involved only a small proportion of American troops in Europe, those

of the Air Force based in Great Britain, the rates for neuropsychiatric disease were fairly stable and at a satisfactory level. For the whole experience, admissions for this cause constituted about 7% of all disease. The influence of major field operations is evident in the rise in frequency that took place in the summer of 1944 when the continent of Europe was invaded. The excess incidence was as sharply defined, and interjected as precipitously, as that of any epidemic of acute upper respiratory infection or other communi-

TABLE 1.—DEATHS FROM DISEASE AND DEATHS FROM BATTLE CASUALTIES IN THE PRINCIPAL WARS OF THE PAST 100 YEARS

War	Deaths		
	Disease	Battle	Disease : Battle
Mexican War, 1846-47 (United States) ¹	10,986	1,549	7.03:1
Crimean War, 1854-56 (French) ⁹	70,000	7,500	9 33:1
Civil War, 1861-65 (Union Troops) ²⁴	186,216	76,216	2 44:1
Danish War, 1864 (German) ¹¹	310	738	0 42:1
(Danish) ¹²	820	1,446	1 57:1
German War, 1866 (German) ¹⁷	5,219	4,008	1 30:1
Franco-Prussian War, 1870-71 (German) ^{9,23}	14,904	17,225	0 86:1
Russo-Turkish War, 1877-78 ¹⁶	80,000	20,000	4 00:1
Sino-Japanese War, 1894-95 (Japanese) ⁹	15,850	1,311	12 09:1
Spanish-American War, 1898 (United States) ¹⁵	4,795	379	12 65:1
Philippine Insurrection, 1898-1902 (United States) ¹⁵	4,409	1,036	4.26:1
Boer War, 1899-1901 (British) ^{3a,6}	11,377	6,425	1 77:1
War in South-West Africa, 1904-07 (German) ¹⁷	689	802	0 86:1
Russo-Japanese War, 1904-05 (Japanese) ¹⁷	21,802	58,257	0 37:1
(Russian, less Port Arthur) ⁹	18,830	23,008	0 82:1
World War I, 1914-18 (French) ⁵	1,750,000	924,700	1 89:1
(German) ⁶	155,013	1,531,048	0 10:1
(United States, all troops) ²³	58,119	50,385	1 11:1
(United States, A.E.F. Europe) ²³	21,314	50,385	0.42:1
World War II, 1939-45 (United States, European Theater) ⁸	1,432	122,384	0.012:1

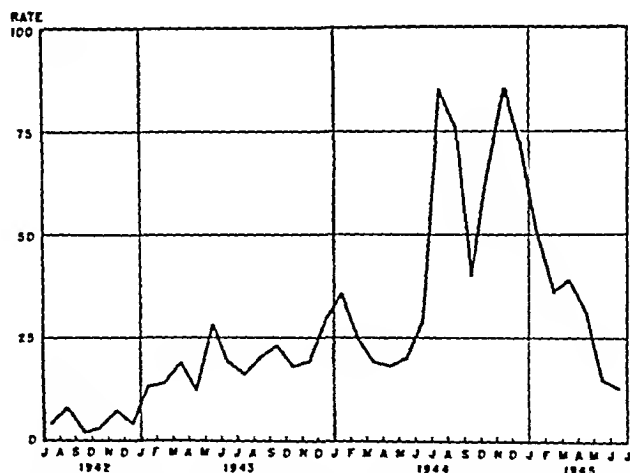


FIG. 3.—Neuropsychiatric conditions, admissions to hospitals and quarters, European Theater of Operations, U. S. Army, rate per 1000 strength per annum, by months, July 1942 to June 1945 inclusive.

cable disease. In July 1944, about one-fourth of medical admissions were of this class. As the pressure of assault operations was relieved, the frequency of neuropsychiatric conditions declined as promptly as it had arisen; despite the fact that this was a period of relatively active field operations marked by the rush across France and the approach to the German border. The outstanding difference was that this was a conquering army, with rapid and successful advance against an enemy that offered little resistance.

The frequency of neuropsychiatric disease again rose sharply when the attack was resumed in November; and a second peak of excess incidence duplicating that of the first was associated with the stubborn active defense action brought about by the Battle of the Bulge. Thereafter, the rates declined progressively and in marked degree, despite the active offensive action of February, March and April, when the Rhineland was invaded and the Inner Reich eventually occupied. The rates then were little more than during the relatively peaceful days in Great Britain before the continental campaign got under way.

The changing character of losses from disease is equally well illustrated by the kinds of conditions that entered into mortality rates from that cause in the European Theater. Considering the entire period of operations, 5 more deaths were recorded from alcohol poisoning than from all communicable processes combined, to include not only the usual epidemic diseases, but all other infectious processes such as tuberculosis and the pneumonias.

By either of the 2 principal criteria by which the effects of disease are judged, mortality and morbidity, the communicable diseases have decreased significantly as a factor of importance in military operations. Qualitatively the non-communicable processes have attained a significance out of proportion to previous experience. The effect that these changes have had on the total losses from disease are illustrated to advantage by an exam-

ination of the experience of the European Theater of Operations during World War II, as compared with the American Expeditionary Forces of World War I.

For each of the 4 years that the European Theater was in existence, disease was far and away the most frequent cause of admission to hospital or quarters (Fig. 4). The highest rate was in 1943, the widespread epidemic of influenza that occurred in the autumn of that year being the chief determining factor. The rates from year to year showed little variation, irrespective of whether the battle was fast or slow. A direct correlation between the activity of military operations and the frequency of disease was lacking. The numbers of persons affected were regularly great, since 1 out of 2 soldiers tended to suffer each year some disability from disease of sufficient degree to interfere with military duties. The regularly occurring annual peak of incidence in late autumn or early winter (Fig. 5) serves to demonstrate the overwhelming importance of acute upper respiratory infection as the dominant factor in morbidity for this class of disability.

No particular significance attaches to the experience of the first 2 years of the European Theater. The morbidity rates for disease were in all respects satisfactory and the health record good. The striking feature becomes evident in respect to the last 2 years. During the height of the campaign, which started in the middle of 1944 and ended in the early summer of 1945, the morbidity rates for disease as judged by admission to hospital and quarters was at a lower level (Fig. 5) than at any other time during the war. Proverbially and throughout the history of wars this is the time when losses have been great. Granted that many soldiers will not report sick during the height of military operations, and particularly in time of advance, nevertheless the fact that so few were seriously disabled by disease is perhaps the clearest evidence that could be advanced of the progress that has been

made in environmental sanitation and in the practice of preventive measures.

While disease ranked first among the 3 major categories of military casualties as a cause of disability, it was the least important as a cause of death. The absolute rate, 0.5 per 1000 strength per year, was inconsequential when compared with death rates for disease in other wars of this country, or indeed within the history of warfare.

strong second place in 1918 to a good third in World War II. Deaths from non-battle injuries in the recent war exceeded deaths from disease in a greater proportion than deaths from battle casualties had exceeded disease in World War I. Comparing directly deaths from battle casualties and disease in the 2 wars, the ratio in the European phase of World War I was slightly better than 2 to 1; in the second war about 92 to 1.

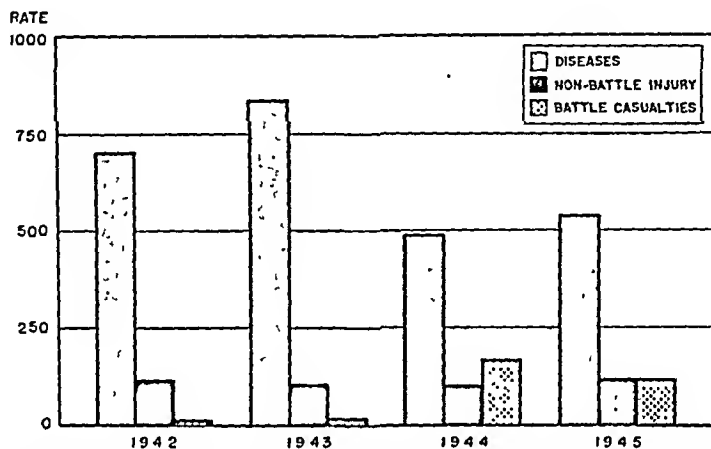


FIG. 4.—Admissions to hospitals and quarters, all causes, European Theater of Operations, U. S. Army, rates per 1000 strength *per annum*, February 1942 to June 1945 inclusive.

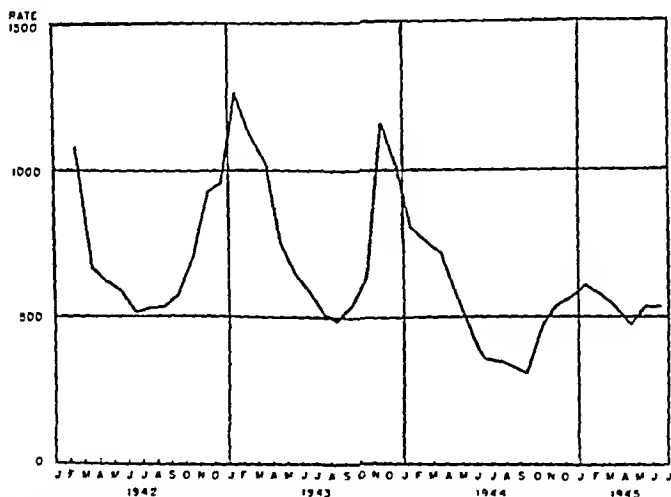


FIG. 5.—All diseases, admissions to hospitals and quarters, European Theater of Operations, U. S. Army, rates per 1000 strength *per annum*, by month February 1942 to June 1945 inclusive.

The 2 European Wars of the United States offer an opportunity for comparison of the changing trends in causes of death among military casualties (Fig. 6). Battle casualties were the principal cause in both instances, but disease dropped from a

Losses from battle casualties are difficult to compare because so much depends upon the type of campaign and the development of weapons of war. These 2 campaigns were fought in the same general region and against the same enemy; to

that extent the comparison is reasonable. At any rate, deaths from battle casualties were proportionately less in World War II than in World War I and it is reasonable to interpret that difference as related to improved methods of medical care. Expectedly the active open warfare of the more recent experience would lead to a greater proportion of casualties than the static trench warfare which characterized

the greater hazards associated with a more highly mechanized warfare.

The experience thus far presented in respect to the casualties resulting from disease in World War II have related wholly to the European Theater of Operations. The experience for all 9 theaters of operation through June of 1945 is presented in Table 2, but carries no suggestion of a comparison of results or an

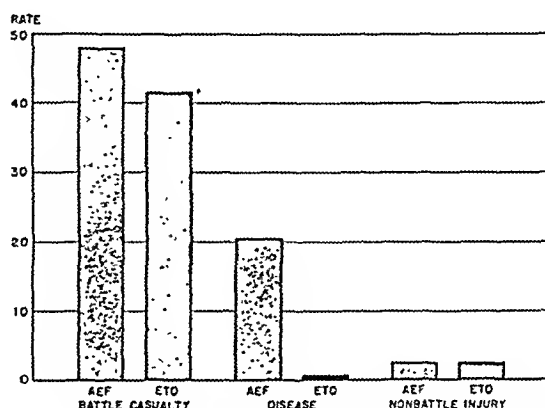


FIG. 6.—Causes of death in World Wars I and II, troops of the AEF (April 1917 to December 1918 inclusive) and of the European Theater of Operations (February 1947 to June 1945 inclusive), U. S. Army, average rates per 1000 strength per annum.

TABLE 2.—ALL DISEASES, ADMISSIONS TO HOSPITALS AND QUARTERS, TOTAL ARMY, CONTINENTAL UNITED STATES AND THEATERS OF OPERATIONS, U. S. ARMY (CASES AND RATES PER 1000 STRENGTH PER ANNUM, BY YEARS, JANUARY 1942 TO JUNE 1945, INCLUSIVE).

Theater	Total		1942		1943		1944		1945	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Total Army	14,120,214	667	2,047,606	671	5,163,760	768	4,550,658	606	2,358,190	609
Continental United States	8,578,265	653	1,699,134	699	3,793,588	739	2,261,800	561	823,743	571
Total Overseas	5,541,949	690	348,472	679	1,370,172	860	2,288,858	654	1,534,447	631
Africa-Middle East	123,336	946	7,783	1356	59,073	1107	42,468	896	14,012	587
China-Burma-India	308,806	929	5,951	1046	45,636	991	171,716	1077	85,503	707
Southwest Pacific	1,117,120	926	55,751	832	204,267	1046	465,289	840	391,813	1006
Mediterranean	1,148,934	849	9,618	451	406,619	943	558,051	846	174,646	726
South America	235,832	676	84,864	825	82,748	684	46,448	540	21,772	558
Pacific Ocean Area	626,954	600	72,812	494	239,851	813	221,457	561	92,834	448
Alaska	155,041	571	33,564	665	71,615	624	39,766	478	10,096	431
Europe	1,735,263	546	50,851	700	221,078	837	725,437	492	737,867	538
North America	90,663	534	27,248	672	39,285	548	18,226	433	5,904	352

Source: Medical Statistics Division, Office of The Surgeon-General, War Department, Washington, D. C.

so much of operations in 1918. While the differences in death rates from battle casualties during the 2 wars is not great, that in respect to disease is most striking. The losses in 1942-45 were but a fraction of those of the previous experience, essentially one-fortieth. Only in respect to non-battle injuries did the death rates of World War II rival those of World War I. The rates were almost identical despite

attempted measurement of accomplishment in these several areas of military activity. It is wholly evident that losses from disease are subject to great variation according to differences in environment, the kinds of risk to which troops are subjected, the prevailing health hazards, and the prevalence of particular communicable diseases. It is, however, a matter of satisfaction that where environ-

mental conditions were similar and risks comparable, the morbidity rates for disease in overseas theaters compared favorably with those experienced by troops stationed in continental United States, which was 653 per 1000 strength *per annum*. Four theaters actually had better rates, although allowance must be made for the problems associated with recruits in the Zone of the Interior, and the greater resistance of seasoned troops who went overseas.

The North American Theater had the best morbidity rate for disease of all forms, 534 per 1000 strength per year. The European Theater, the largest in respect to troop strength, was next. The highest morbidity was experienced by troops of the Africa-Middle East Theater, followed closely by those stationed in the China-Burma-India area and in the South-West Pacific. The admittedly greater hazard of the Mediterranean area of Europe as contrasted with northwest Europe is reflected in average annual rates for disease of 849 and 546 per 1000 strength per year.

The analysis of the component causes which served to determine these rates, and a comparison of experience between theaters, is beyond the scope or intent of this presentation. The results universally obtained in respect to a particular disease long recognized as a peculiar hazard of war, are nevertheless so striking as to deserve special mention. In the European Theater of Operations where battle casualties were more numerous than in any other theater, both the mortality and the morbidity rates for tetanus were less than among troops stationed in continental United States, thousands of miles from a field of battle. The almost unbelievably good results, a single case and a single death during the whole period of operations in Europe, are attributable to the remarkable effectiveness of active immunization brought about by tetanus toxoid. No soldier left America without immunization and the greater rates in the Zone of the Interior, of themselves inconsequential, were related to tetanus infec-

tion among recruits before immunization had been accomplished. The detailed circumstances of this experience in all theaters of operation have been presented by Long and Sartwell.¹⁴

World War II involved more men and extended over a greater geographical area than any other in history. The successful result that accrued to the American arms was influenced in forceful degree by the action of favorable casualty rates for disease previously without precedent. The overall results speak for themselves. The extent to which disease influenced individual campaigns remains to be examined, first in respect to long-term strategic action and secondly as an immediate tactical influence.

STRATEGIC INFLUENCE OF DISEASE. Rarely does the practice of epidemiology on the grand scale reach such potentialities as in war. The epidemic of typhus fever that eventually involved American troops in Germany in 1945 constitutes an outstanding example of the strategic influence of disease in field operations. The epidemic was evident well in advance of the time that it became an immediate military problem, with the result that plans and an organization for meeting the situation got under way as early as 1941.

The probable situation at different times in the projected course of military operations was analyzed in detail. Arrangements for a cordon sanitaire along the Rhine River with tentative ports of entry were set up 3 years before an American soldier crossed that river. A significant change in procedure was incorporated in the plan in 1944 when the value of the newly developed insecticide DDT became evident. Unit responsibility for control measures in the particular area of influence was recognized as the fundamental approach. Provision was made at theater and army echelons for teams trained in diagnostic and insect control procedures to furnish the necessary aid and consultation to unit surgeons. The proper administration of the cordon

sanitaire was made the responsibility of the army group.

Typhus was found in Germany in March 1945 as anticipated, in all a total of 17,000 cases.¹ The number of secondary infections was surprisingly few. The outbreak was eliminated within 3 months. During this time only 3 American soldiers contracted the disease, 2 of them physicians engaged in typhus control. The results contrast with what took place in 1918, although at that time material progress had already been made in knowledge of this epidemic disease and in measures for its control. More than 5,000,000 persons¹³ had typhus fever in Russia alone⁷ and deaths have been estimated at 2,000,000; in Serbia¹⁰ essentially one-fifth of the population was involved in the epidemic, with 150,000 deaths²² in a 6 month period of 1915. The potentialities for a similar major epidemic in 1945 were decidedly great, for the existing circumstances were not dissimilar from those of 1918. The difference in result was determined by the advances in technical knowledge that had taken place within recent years, and the new measures for control that were provided. It depended upon careful planning at staff levels, adequate provision of supplies, organization of the special United States of America Typhus Commission, and finally the thorough mobilization of the field medical services who did the work of control. From a strategic standpoint, the casualties from this cause among military personnel were negligible. Not a single death occurred from a disease recognized as one of the great pestilences of man, and characterized by a notably high fatality. Still more important was the absence of any interference with military operations at a critical time in the developing final offensive. The army suffered no significant losses itself, nor was it called upon because of typhus to provide medical and other care to an overwhelmed civilian population of occupied territory.

Malaria in the Southwest Pacific constituted a strategic problem of equal im-

portance to that of typhus fever in Europe. Advance planning had likewise been concerned with the provision of malaria control supplies, the development of method, and the training of personnel to combat this communicable disease. The early years of operations in that theater were attended with shipping difficulties. It is a function of theater authority to allot tonnage and a choice had to be made among the various classes of supplies assembled at ports of debarkation. The choice was made with the result that troops taking part in the early campaigns in the Solomons and in New Guinea were without sufficient malaria control supplies and lacked specially trained control organizations. The casualties from malaria were high. In the South Pacific Area the attack rate for malaria reached 696 per 1000 per year in August 1943. In the Southwest Pacific Theater the attack rate early that year exceeded 400. Four American and 2 Australian Divisions were incapacitated for periods of more than 6 months. At one time more than 30% of available beds in the Southwest Pacific Theater were occupied by malarial patients. Subsequently the situation improved greatly. Survey and control units were assigned to field control, the necessary supplies were shipped and strong emphasis was placed by command on the improvement of malaria discipline among troops. The morbidity rate for malaria declined steadily during the latter half of 1943, and in 1944, so that by 1945 the attack rate was less than 40 cases per 1000 troop strength per year in the better areas. The extent of the problem is indicated by the loss of 800,000 man days from malaria in the Southwest Pacific Theater in 1943, this constituting a fourth of the losses from all disease. The proportion was reduced to 5% in 1944; and the old ratio of greater losses from disease than from battle casualties again returned to the more favorable circumstance which characterizes modern warfare. The strategic

problem was met, but after avoidable losses.

The principle in facing a problem where the influence of disease is involved, is a question of how many effectives can be maintained in the line. Medical weapons and medical supplies may be as important a consideration as the number of troops made available or the basic military supplies of ammunition, rations and motor fuel.

little variation (Fig. 7). The rate for the year 1944 was actually the best of the 4 years despite the autumn campaign in France and appreciable losses in the last 2 months of that year from trench foot, a major item in the category of non-battle injury. The excess rate for 1945 was almost wholly of that origin and yet the rate for the year was not greatly in excess of the first training year of 1942.

The attack rate for disease was much

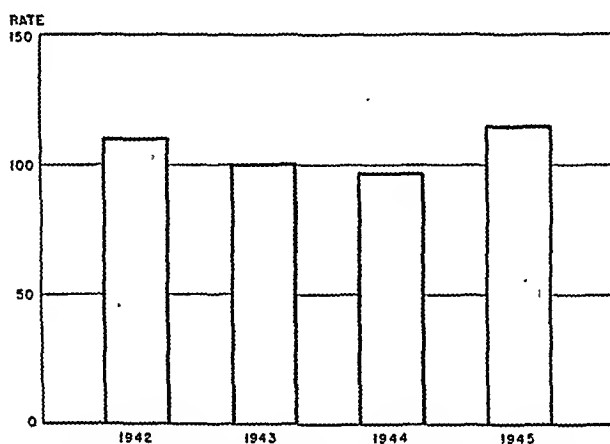


FIG. 7.—Non-battle injuries, admissions to hospitals and quarters, European Theater of Operations, U. S. Army, rates per 1000 strength *per annum*, February 1942 to June 1945 inclusive.

TABLE 3.—NON-BATTLE INJURIES, ADMISSIONS TO HOSPITALS AND QUARTERS, TOTAL ARMY, CONTINENTAL UNITED STATES, AND THEATERS OF OPERATIONS, U. S. ARMY (CASES AND RATES PER 1000 STRENGTH, PER ANNUM, BY YEARS, JANUARY 1942 TO JUNE 1945, INCLUSIVE)

Theater	Total		1942		1943		1944		1945	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Total Army	1,921,342	91	294,288	96	624,849	93	666,209	89	335,996	87
Continental United States	987,163	75	230,366	91	412,655	80	270,536	67	73,606	51
Total Overseas	934,179	116	63,922	125	212,194	133	395,673	113	262,390	108
Alaska	41,341	152	7,619	152	20,852	182	10,558	127	2,312	99
Southwest Pacific	166,758	138	11,963	178	33,317	171	77,046	139	44,432	114
Mediterranean	179,581	133	2,040	96	64,075	149	91,063	138	22,403	93
North America	21,160	125	6,330	156	9,747	136	4,065	96	1,018	66
Africa-Middle East	14,679	113	928	162	9,469	140	4,712	99	1,570	66
Pacific Ocean Area	111,366	107	15,379	104	33,590	114	43,648	111	18,749	90
European	335,445	105	8,023	110	26,497	100	143,201	97	157,724	115
China-Burma-India	31,541	95	460	81	3,893	84	15,385	96	11,803	98
South America	32,305	93	11,180	109	12,754	105	5,995	70	2,379	61

Source: Medical Statistics Division, Office of The Surgeon-General, War Department, Washington, D. C.

NON-BATTLE INJURY AS A STRATEGIC AND TACTICAL INFLUENCE. The experience of the European Theater of Operations may be taken in illustration of the regularity with which losses from this class of military casualty occur. Irrespective of whether operations relate to a time of training or to an active campaign in the field, the number of men lost by reason of non-battle injury is subject to

greater than that for non-battle injury, varying from a ratio of 8 to 1 in the most unfavorable year to a relationship of 5 to 1 under the most favorable conditions (Fig. 4). The difference between the 2 conditions is less marked when judged on the basis of the resulting non-effectiveness, since the period of disability from injury is longer than that for disease (Fig. 2).

A comparison of morbidity rates for non-battle injury in the several theaters of operation shows a variation in experience considerably less marked than for disease (Table 3). Without exception, casualties from non-battle injury were more frequent in theaters of operation than in continental United States, since no theater approached the average rate of 75 per 1000 strength per year established by troops of the Zone of the Interior. The influence of environment on the record attained was strongly evident. The Alas-

under a given set of conditions can be influenced by the extent to which preventive measures are applied. The important component conditions of motor accidents and trench foot are decidedly in point.

Trench foot in Attu, in Cassino and in the European Theater was a strategic problem of preventive medicine. The condition is an accompaniment of campaigns in wet cold climates. In a given week, in November 1944, 3000 cases occurred in a single field army. In the months that followed, all combat troops of the

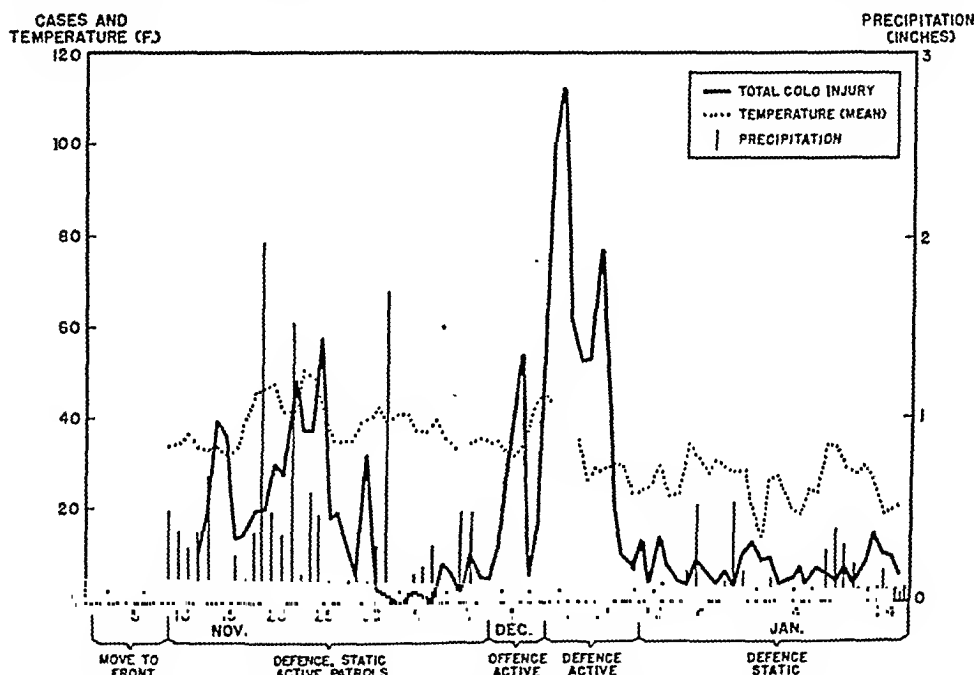


FIG. 8.—Cold injury in an infantry division, frequency of cases by type of military operation, temperature ($^{\circ}$ F.) and precipitation in inches.

kan Theater with 1 of the best rates for disease had the highest rate for non-battle injuries, and conversely the China-Burma-India Theater, with a rate of 929 per 1000 per year for disease, had the admirable record of 95 for non-battle injuries. Again it is to be emphasized that no direct comparison between theaters can be made on the basis of these crude rates because environmental and tactical conditions varied greatly. The important consideration is that these are in large part preventable conditions, and the rate

European Theater were involved in varying degree.⁸ Field control was strictly an epidemiologic problem. Attack rates were shown to bear a definite relationship to the existing tactical situation. The risk varied as troops were on the offense, engaged in holding actions, under static conditions, or in rest areas. The kind of weather exerted an influence, likewise the character and amount of clothing and equipment. Qualities of the terrain could be demonstrated as a contributing factor and of decided significance were the

methods of management of troops. The incidence was by no means uniform. Certain armies, divisions, regiments and even battalions suffered inordinately in comparison with neighboring units operating under similar environmental circumstances. Riflemen were affected beyond all other occupational army groups, with more than 90% of cases in this important component of the ground forces. The importance of this circumstance becomes evident when translated into terms of effective combat strength. A loss of 15,000 men from trench foot is seemingly the equivalent of 1 division and yet with 4000 riflemen to a division and 90% of the casualties within that group, the actual loss is 4 effective fighting divisions. The contributing causes of the condition and its incidence varied from place to place and from time to time. The principle of prevention is evident—an epidemiologic analysis of cause and effect (Fig. 8) and a fitting of control measures to the individual circumstances.

Three times in the course of World War II, trench foot was encountered as a strategic problem and 3 times the losses were beyond calculated risk or reasonable expectancy. The invasion of the Japanese mainland would have presented a fourth situation, for the environmental conditions predisposed in a degree comparable to those of Italy and northwest Europe. The combined opinion and effort of several arms and services went into the development and initiation of a plan which included the chief considerations of clothing and supplies, education of the individual soldier, the organization of special trench foot control units, and the administrative action of command. What was done never came to test, for hostilities ended before Japan was invaded. It behooves any future planning group concerned with a campaign in wet cold climates to review that plan.

Summary. The strategic influences of disease on military operations are understood to include those medical problems continuously present and existing by

reason of environmental or ecologic influences peculiar to a given situation. They may represent problems of disease, as with malaria; or of injury, as indicated by the continually existing accident problem. Conversely, strategic problems may be temporary and unusual, but not unexpected. They are the carefully defined results of an anticipated change in ecologic equilibrium. When American soldiers set out for the Normandy beaches in June 1944, difficulties in respect to trench foot were certain to occur the following autumn and winter, with the extent of losses dependent upon the adequacy of plans and the sufficiency of supplies for prevention and control. The counterpart in respect to disease is illustrated by typhus fever in Europe, existing under conditions incident to war, although a disease normally absent.

Medical problems of tactical significance are those relating to the immediate situation. They may be so far-reaching as to involve most of the members of a military community. More commonly they are localized and sometimes highly individual. Under all circumstances they require prompt analysis of the situation and the institution of specifically directed control measures. The suddenly developing epidemic of influenza in Great Britain in 1943 was an example of a widespread tactical problem in military preventive medicine. The more usual illustration was that of an excess accident rate in a Quartermaster depot, the abnormal prevalence of venereal disease at a port of embarkation, or the series of peculiar illnesses at a chemical warfare service impregnation plant. These are the problems of the day and find complete analogy in similar occurrences of civilian communities.

The utilization of the medical services of a combat force to meet the strategic and tactical problems introduced into military operations by reason of disease requires more than adequate care of the sick and wounded. Many of the more important problems are essentially mat-

ters of preventive medicine. They are of 2 kinds: the group problems of the military community and the health problems that relate to the individual soldier. The group problems extend much farther than the control of epidemics and the management of communicable disease. Under modern conditions the infections become progressively less important and concomitantly non-communicable processes attain increasing significance—injury, accidents, trench foot—and a variety of nutritional, neuropsychiatric and other diseases, unrelated to communicability and yet of epidemiologic importance.

The health problems of the individual soldier rate equal importance with strictly group problems, since clothing, housing, nutrition and psychologic management act importantly in decreasing the slow attrition from disease and disability, which if exaggerated can approach in losses those that result from epidemic disease.

A basic principle in minimizing the adverse strategic and tactical influences of disease on military operations rests in a protective maintenance applied to men as well as to machine. And that is preventive medicine in its simplest terms.

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PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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ORAL IMMUNIZATION

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MANKIND seems to enjoy placing a wide variety of objects into the mouth, but displays a widespread dislike of the needle puncture. From these impulses, which are perhaps primordial, may derive much of the preference likely to be shown for oral ingestion rather than hypodermic injection of specific therapeutic and prophylactic substances, whether narcotics, endocrines, vitamins, sulfonamides, antibiotics or immunizing agents.

Sounder reasons for this preference may, of course, be advanced. For instance, peroral administration is simpler and cheaper, involving neither apparatus nor professional attendants. The obviation of local reactions at the injected site is also important, especially when dealing with sick or enfeebled patients, with subjects allergic to some bacterial product, or whenever it is essential that a minimum of hours should be lost from work, *e. g.*, by doctors, nurses and persons in the armed forces. Again, the possibility of a quicker rate of immunity development embodies many obvious advantages. Enthusiasm among immunologists for oral vaccination has been discontinuous and scattered, but understanding of its limitations has been only tentative. Hence, even the most hardened sceptic may experience at times a powerful attraction to the faith that an effective multiple antigen might be devised which could be swallowed by anyone whenever the occasion demanded;

while a few of the more optimistic appear unable to exorcise themselves from a vision of some omnivalent pill, to be put out in a bottle discrete in size, elegant in shape, and of various styles to match the bedroom dressing-table décor of all smart people! These considerations, bolstered by the undeniable evidence that certain microorganisms or their toxins customarily gain access to the human body through the gastro-intestinal tract, perhaps account for the recurrent interest shown in oral immunization by reputable investigators. They no doubt also serve as inspiration for the unflagging eagerness of some manufacturers to feed the gullible with specious half-truths and impotent preparations.

Counterbalancing the possible advantages of the oral route are certain *a priori* handicaps to its effective use. The vagaries of human nature could obviously make the very convenience of this method an inducement for taking the medicine only as the spirit moved, rather than according to prescription; and the community, no less than the individual, would suffer the consequences of such sporadic and unrecorded self-administration. The already high incidence of unfulfilled obligations to seek specific protection against infection in the interests of one's own and one's neighbor's health might climb rather than fall; while the present meager statistics on the immunity status of given populations would be

further vitiated. Again, licensing authorities face imposing difficulties in attempting to check the composition and antigenic properties of a vaccine to be administered in pill, capsule or lozenge form, or of an elixir alleged to contain some bacterial metabolite of extraordinarily subtle virtue. In fact, it is no prejudgment of the issue to state that advocacy of oral immunization tempts the streak of charlatanism present in too many of us.

The Plan of Approach. However, the main purposes of this review are not to discuss the pros and cons of immunization *per os* in terms of psychologic and commercial problems involved, but rather to assess the feasibility and efficiency of the method as judged by evidence presented in the extensive and often conflicting literature; and also, to attempt a brief elucidation, in terms of modern immunologic conceptions, of the factors contributing to whatever theoretical and practical inadequacies may become apparent. The topic will not be reviewed from a narrowly historical or evolutionary standpoint; nor can reference be made to every publication bearing upon it. In the earlier years, a majority of reports on oral immunization appeared in the foreign journals, chiefly French and German. In some instances, these journals have not been available; in others, records of results which seemed unduly repetitive or trivial have been omitted. Some important work may have been unintentionally overlooked; but an effort has been made to accord fair credit and representation to the more significant contributions, and readers desiring to supplement the bibliography can readily do so by consulting these references.

From the beginning, investigators have tended to acquire interest in oral immunization out of concern with some human or animal infection for which the alimentary canal was believed the customary portal of entry, or the main seat of injury. Pasteur, for instance, made the earliest clear-cut reference to the possibility of immunization by ingestion, in a footnote

to a paper on the etiology of anthrax, presented in 1880 to the Academy of Sciences in Paris, in collaboration with his colleagues Chamberland and Roux.²³ "Chickens that have been given food infected with the microbe of fowl cholera, and do not die, may have been vaccinated. Hence one may ask if one could not manage to vaccinate sheep against anthrax by submitting them previously and gradually to meals infected with the spores of the parasite."

A quarter of a century later, in 1906, Calmette and Guérin,²⁴ having become convinced that tuberculosis of man and animals, even in its pulmonary manifestations, was of intestinal origin, reported that they had thence been led to investigate "if it would be possible to vaccinate animals susceptible to tuberculosis against the natural infection by causing them to absorb through the digestive tract, young, while modified, attenuated or avirulent tubercle bacilli."

Again, Besredka's theory of local immunization largely stemmed from experiments on the problem of infecting mice orally with paratyphoid bacilli. The crucial observation was recorded thus in a paper by himself and Bassèches:¹⁸ "One day, lacking fresh mice for a control experiment, we thought of using a mouse which had received, 1 month previously, paratyphoid bacilli by mouth. Having injected this mouse with a certainly fatal dose of a virulent paratyphoid culture, what was our surprise to find it, next day, gaily chewing its oats as if it had received nothing."

These examples may serve to illustrate the point that there has been all along a disposition to assume that those microorganisms and their toxic metabolites which cause disease by naturally traversing the alimentary tract of man or animals, or which seem to exert their major pathogenic effects thereon, are the ones most likely to prove antigenic when taken by mouth. The validity of this assumption need not be discussed, still less accepted at this stage. But its provisional adop-

tion suggests a convenient order to follow in the main part of this review.

Classification of Pathogenic Agents Under Review. Consideration will first be given to those pathogenic agents to which the term "enterotropic" may, with some reservations, be applied. Succeeding sections will review these agents in turn, arranged roughly according to diminishing degrees of apparent natural affinity for the intestinal tract. Since oral immunization is a process directed against microorganisms or their toxins, rather than against clinical syndromes, the sequence to be followed will be indicated here by listing representatives of each section.

1. *Eberthella typhosa*, *Salmonella paratyphi* B and other members of the *Salmonella* group.

2. *Shigella dysenteriae* (*shigæ*), and other members of the *Shigella* group.

3. *Mycobacterium tuberculosis*.

4. *Clostridium botulinum* toxin, and *Staphylococcus enterotoxin*.

5. *Pasteurella pestis*, *Brucella abortus*, and certain animal pathogens.

6. *Staphylococcus*, *Streptococcus*, and *pneumococcus*

7. Miscellaneous preparations, including mixed "cold" vaccines.

Each of these agents will be scrutinized in the light of the relevant reports. Critical comments will only be interjected where these seem necessary for proper interpretation of results. Criticisms of a general nature will mostly be reserved for the final discussion.

EBERTHELLA-SALMONELLA ORGANISMS. More widespread use of antityphoid inoculations has been delayed by disputes about the significance of the various humoral antibodies which may be detectable after vaccination, by failure to recognize that immunity is in any event relative rather than absolute, and by the argument that improved standards of community sanitation and personal hygiene have been of paramount importance in reducing the incidence of typhoid fever in recent decades. Faulty methods of manufacture, and the administration of inadequate dosages of typhoid vaccine, have also led

to disappointment. Nevertheless, few authorities now remain unconvinced of the value of antityphoid inoculations—particularly in time of war and other emergencies, or in areas where sanitary standards are low. A good summary of the earlier statistical data bearing on the efficacy of this practice has been provided by Harvey.⁸⁷

The reactions liable to follow subcutaneous injection of the vaccine are admittedly a serious handicap. Indeed, the recurrent efforts made to provoke effective immunity by some form of peroral vaccination largely stem from a desire to avoid these untoward reactions. The results obtained by earlier workers were on the whole so disappointing that interest in this mode of administration lapsed, until revived by Besredka's vigorous championship of the local immunity concept. He visualized oral vaccination against the enteric group of infections as the most important and logical application of his principles. His contentions will later be critically appraised.

Typhoid fever is now recognized as one of a large group of related infections. The similarities in epidemiologic and immunologic characteristics between typhoid and paratyphoid A and B fevers led to the custom of adding *S. paratyphosa* A and B to the suspension of *Eb. typhosa* in the preparation of the mixture known as T.A.B. vaccine. More recently, these 3 microorganisms have been assigned a place in the still-enlarging *Salmonella* group, where they are linked, under the Kauffmann-White scheme of classification, with some 150 other known types of human or animal pathogens, possessing certain cultural, biochemical and agglutinogenic properties in common. The many reports of earlier workers on oral immunization against typhoid and paratyphoid fevers will therefore be considered together with the few reports involving such related types as *S. typhi murium*.

In general, reports on oral immunization against enteric infections have furnished evidence of the following types: (i) Levels

of titratable antibodies attained in experimental animals or man following vaccination.

(ii) Protection displayed by vaccinated laboratory animals or man against the homologous pathogenic agent.

(iii) Statistical data on specific resistance to infection following vaccination of population groups in endemic or epidemic areas.

The first 2 of these headings may conveniently be merged for present purposes.

Effect of Vaccination per Os on Specific Antibody Formation and Immunity Development. In 1904, Wright¹⁵⁵ reported administered heat-killed cultures of *Eb. typhosa* to 7 persons by mouth, 3 of whom developed a marked increase in the bactericidal power of their blood, while 4 showed a decrease. One person complained of diarrhea and constitutional disturbances, but the others suffered no reaction. In the same year, Tehitckine¹⁵⁹ fed live typhoid cultures to rabbits, and noted the appearance of agglutinins, complement fixing bodies, and precipitins in the blood serum. Sera from such animals gave no passive protection. Ingested typhoid culture filtrates sometimes evoked weak agglutinin production in rabbits. Loeffler¹⁶⁵ reported in 1906 having conferred some measure of immunity upon white mice and field mice, which had been fed repeatedly with heat-killed cultures of *S. typhi murium*. Some of these mice proved resistant to virulent, living cultures given orally, but not to similar cultures injected subcutaneously or intraperitoneally. Since the orally vaccinated field mice showed no agglutinin formation, Loeffler concluded that their acquired immunity was not general, but localized in the intestinal mucosa. Two years later, Wolf¹⁵⁴ obtained essentially similar results with white mice, which developed some resistance to ingestion of virulent cultures of *S. paratyphi B*, after prolonged feeding with broth cultures of living but avirulent strains. He noted that specific bacteriolysins developed, but no agglutinins.

In 1910, Leishman¹⁵⁴ reported discour-

aging results in man from attempts at peroral immunization with typhoid vaccine. His colleague, Major Harrison, had "endeavored to guide dead typhoid bacteria past the dangers of the stomach into the intestine," by administering to fellow officers in the British Army, pills containing typhoid bacilli suspended in a matrix of fat and stearin. Others were given the bacilli suspended in lard, in gelatin capsules. Some subjects had gastric disturbances, and the effects upon the bactericidal power of the blood were irregular.

Other workers of this period reported somewhat more promising results with laboratory animals. Kutscher and Meinicke,¹⁶⁰ for instance, in 1906 claimed to have immunized guinea pigs against *S. paratyphi B* and *S. enteritidis* by feeding a single large meal of parsnip pulp mixed with a 24 hour broth culture of either one of these microorganisms. Four weeks after the meal, most of these animals were resistant to 1000 to 10,000 minimal lethal doses injected intraperitoneally. Similar experiments with typhoid bacilli were unsuccessful. These workers also fed young calves, sheep, goats, dogs and a horse with 1 large dose of paratyphoid culture. No agglutinins developed. Again Hida and Toyoda⁹⁰ gave guinea pigs by mouth capsules containing typhoid, dysentery or cholera bacilli predigested with trypsin and pepsin, and noted development of serum agglutinins and bacteriolysins. Ingestion of heat-killed cultures provoked no antibody formation. Shiga,¹⁶¹ on the other hand, demonstrated some immunity development in rabbits given heat-killed paratyphoid cultures by mouth. Moreover, Brückner²² reported that mice given several daily ingestions of an avirulent culture of *S. paratyphi B* subsequently withstood a normally lethal subcutaneous dose of virulent culture. Disagreeing with Loeffler, he contended that intensive vaccination *per os* could give rise to a true general immunity.

In 1911, Metchnikoff and Besredka,¹¹³ having shown that typhoid fever could be transmitted to chimpanzees, attempted to

vaccinate 1 of these anthropoids by giving orally on 2 occasions, 15 cc. of heat-killed *Eb. typhosa* culture. When challenged 11 days later with a large dose of living typhoid bacilli, sufficient to cause severe illness in a control ape, the vaccinated animal developed only a mild pyrexia. However, an attempt to reproduce this result was unsuccessful. Simultaneously, Courmont and Roehaix⁴⁵ vaccinated goats and rabbits orally and rectally, the latter route being better tolerated. Three doses of a polyvalent suspension of 8 day, heat-killed cultures of *Eb. typhosa* were administered rectally, at intervals of a few days, each dose being 100 cc. for rabbits, and 250 cc. for goats. Agglutinating, bacteriolytic and bactericidal properties soon appeared in the serum, but the titer of agglutinins did not rise above 1:50. Fifteen days after the last rectal instillation of vaccine, rabbits were able to resist, almost without symptom, an intravenous injection of virulent *Eb. typhosa* which killed controls in 28 hours. An unstated number of human subjects also received 3 doses of 100 cc. of vaccine per rectum, at 5 day intervals. There were no unfavorable reactions, and circulating antibodies appeared after the 10th day. Courmont and Roehaix⁴⁶ soon afterwards observed that rabbits vaccinated rectally resisted typhoid "toxin," comprising an 8 day culture of *Eb. typhosa* heated to 53° C., in a dosage which killed normal rabbits within a few hours. The serum of vaccinated animals neutralized the "toxin" when mixed therewith.

In 1914, Lumière and Chevrotier¹⁰⁹ reported experiments with a powdered form of polyvalent vaccine, prepared from a mixture of washed, centrifuged and dried typhoid, paratyphoid, and coliform bacilli. The product, termed "entéro-vaccin," was administered in keratin capsules to guinea pigs, rabbits and humans, without any resulting fever, diarrhea or other reactions of the types encountered by Courmont and Roehaix. Four months after receiving by mouth a total dosage of 3 billion bacilli per kg., taken in 3 por-

tions at 8 day intervals, guinea pigs and rabbits showed a definite and lasting immunity against a normally fatal intravenous injection of any of these organisms. The enterovaccine of Lumière and Chevrotier was soon submitted to trial by Dubarry⁶¹ on a large number of war prisoners, none of whom complained of any ill-effects from the pills. In 1923, in a valuable review of vaccination by the buccal route, Calmette²⁴ stated that many physicians in France had used enterovaccines, and that in a number of cases circulating agglutinins had developed.

Besredka's Animal Experiments on Oral Immunization. In 1918, Besredka and Bassèhes¹⁸ reported that mice acquired a specific immunity from paratyphoid bacilli given by mouth. This immunity developed slowly, and was slight and transitory unless the mice ingested living cultures. The titratable antibodies were not mentioned. This paper, and another published by Besredka¹¹ soon afterward, initiated a series of publications which greatly influenced conceptions of immunity, particularly as regards oral immunization against enteric infections.

Besredka noted that rabbits became more susceptible to living paratyphoid cultures given by mouth or intravenously after previous ingestion of ox-bile. He asserted that the bile caused desquamation of the intestinal mucosa, thus facilitating absorption of the bacilli; and he deduced that the natural immunity of rabbits to orally administered paratyphoid bacilli was localized in that mucosa. Moreover, although a normal rabbit gained no protection against paratyphoid bacilli from swallowing killed cultures, it became "parfaitement vacciné" after previous sensitization with bile, and was then refractory to bacilli introduced by mouth or intravenously. Since this acquired immunity was established in 3 to 4 days, Besredka held that participation of antibodies in its mechanism was excluded. It in fact also be localized.

Besredka soon extended his conceptions to cover problems of susceptibility and

resistance of the rabbit to experimental infection with Shiga dysentery bacilli,^{12,14} and typhoid bacilli.^{13,15} He now urged oral vaccination for human groups exposed to typhoid and paratyphoid fevers and to bacillary dysentery; arguing that a maximum defensive response should be evoked in the intestinal mucous membrane when microbes reached there directly. Thereafter, a formidable body of doctrine, and a queerly confused terminology, burgeoned on shallow-rooted experimental data, until by 1927 the theory of local immunization had been extended by Besredka¹⁷ to embrace many types of infections besides those having the intestinal tract as customary portal of entry. These claims were soon disputed. Zingher and Soletsky¹⁹⁰ vaccinated bile-prepared rabbits orally with living or dead paratyphoid bacilli, and produced neither agglutinin nor resistance to similar bacilli injected intravenously.

(Besredka¹⁵ had noted that circulating agglutinin titers up to 1:80,000 might be attained in 3 or 4 weeks by rabbits sensitized with bile, and then given a sublethal dose of living paratyphoid bacilli by mouth. These agglutinins had quickly diminished, and did not reappear after subsequent ingestions of culture—an observation which he interpreted as additional proof of the intestinal wall's impermeability in orally vaccinated rabbits, and also of the irrelevance of humoral antibodies.) The only experimental findings of Besredka's which these workers confirmed was that the intravenous dose of living paratyphoid B bacilli required to kill rabbits prepared with bile was only about one-tenth of the lethal dose for unprepared animals. Webster¹⁷⁹ showed in 1922 that roughly the same percentage of mice acquired protection against an orally administered challenge with *S. typhi murium*, irrespective of whether the vaccination route adopted had been peroral (the natural route of infection in mouse typhoid), intrapleural, or intraperitoneal. In other words, the immunity developed was of a general rather than a local nature. Similar con-

clusions were later reached by Greenwood, Topley and Wilson.⁸⁵ In 1923, Webster¹⁸⁰ noted marked individual variation, both in respect to susceptibility to infection, and of agglutinin production in survivors, among mice infected *per os* with a fixed dose of *S. typhi murium*. His findings emphasized the need for employing large groups of animals in experiments of this type, particularly when (as in much of Besredka's work), the host species was normally refractory to the microorganism under test. Pursuing enquiries into the factors influencing host susceptibility in mouse typhoid, Webster¹⁸¹ found that 0.25 cc. of ox-bile given by mouth to mice slightly increased the infection rate, but caused obvious discomfort and diarrhea. Lesser amounts had no effect upon susceptibility, while 0.5 cc. either killed the mice within 24 hours, or made them extremely ill, with severe diarrhea. Webster therefore conceded Besredka's claim that treatment of rabbits with bile promotes absorption of bacteria given *per os* by injuring the intestinal mucosa, but emphasized the excessive toxicity of the dose required to enhance intestinal permeability in mice. Calmette,²¹ in 1923, and Enlows,⁶⁹ in 1925, pointed out the impossibility of administering to man the doses of ox-bile (2 to 3 cc. or more per kg.) used by Besredka as a preliminary to oral vaccination in rabbits.

Further inquiries were launched into the necessity of using bile for effective oral immunization of laboratory animals by Sédan and Herrmann,¹⁸² who reported in 1924 that typhoid infection could be produced in fasting guinea pigs by intramuscular injections of virulent living culture. Similar infection could be induced by much smaller doses injected into non-fasting animals, after 10 cc. of bile had been given orally on each of the 2 days preceding the inoculations. Control animals which had fasted 70 hours were sacrificed, and showed a bile-stained intestinal mucosa, with desquamation, hemorrhage, and absence of mucus—effects resembling, on a smaller scale, those

produced by administration of bile. Burke and Barnes²³ in 1926 confirmed certain of Besredka's findings as regards immunization of rabbits by mouth with typhoid bacilli, but did not use bile. In their hands, oral vaccination proved less effective than subcutaneous inoculation in stimulating agglutinin development; and they considered that mere ease of administration, and reduced toxicity, did not warrant substituting the oral for the subcutaneous method. Again without resorting to bile, Kosmodemiansky⁹⁸ reported in 1928 that heat-killed cultures of *S. paratyphosa* B might prove fatal when given by mouth in large doses to pigeons. Surviving pigeons withstood challenges up to 6 M.L.D. given orally. Immunity sometimes developed after a single ingestion of vaccine, about the 16th day; but the serum showed neither agglutinins, bacteriolysins, nor protective power.

Besredka's Oral Vaccination Methods Applied to Man. In certain parts of the world with an unduly high typhoid fever incidence, some form of Besredka's "vaccin bilié," or "bili-vaccin," was by now being tried out on man. Since reports on field trials of oral immunization with typhoid-paratyphoid vaccine have seldom referred to antibody production, their consideration will be deferred. Findings on the time and degree of antibody development in experimental subjects will first be reviewed.

Hoffstadt and Thompson⁹¹ recorded in considerable detail, in 1929, the development of agglutinins in about 100 university students. Two-thirds of them took 1 cc. of T.A.B. vaccine (about 1 billion typhoid bacilli) before breakfast, for 3 successive days, in a glass of water. The remainder did likewise, but swallowed 2 bile capsules before the first dose. There were no unfavorable reactions. Agglutinins against *Eb. typhosa* developed in 88.5% of the whole group, to titers of 1:600 in some instances. Titers were highest 4 to 5 weeks after vaccination, and then declined irregularly for several months. Slightly more agglutinin pro-

duction was shown by the bile-prepared subjects, and a small control group given the 'customary series of subcutaneous inoculations did still better. The same authors⁹² also found complement fixation and precipitin reactions in an equally high percentage of a smaller group of similarly treated students. Hoffstadt and Martin⁹³ reported results of the same order following replacement of the fluid vaccine by gelatin capsules containing concentrated T.A.B. vaccine, mixed with ox-bile in a starch matrix. Two of 36 subjects reported abdominal reactions. The agglutinin titers attained a lower average level than in the groups taking fluid vaccine.

Good agglutinin responses were also reported, in 1930, by Pijper and Dau,¹²⁷ who gave 40 billion heat-killed, dried *Eb. typhosa*, preceded by a bile pill, on 3 successive days to 9 female patients (7 of them native Bantus) in the Pretoria Mental Hospital. Agglutinins of O type developed in all the treated subjects, the highest titers being reached in about 3 weeks. Pijper¹²⁶ had previously referred to the high frequency of O-agglutinin formation in South Africa. The paper by himself and Dau suggests the more likely explanation that their techniques promoted unduly high readings; for they used live antigen suspensions, and recorded reactions to the last trace, in most of their tests. Krause-Shimkin,⁹⁹ in 1931, tested 46 persons for typhoid agglutinins, before and again three to 5 weeks after receiving 3 daily doses of T.A.B. vaccine, with bile, by mouth. Forty persons who had some time previously received typhoid vaccine, either parenterally or by mouth, developed O-agglutinin titers up to 1:1000, the increases ranging to 20-fold in the former, and to 5-fold in the latter. Six persons not previously vaccinated or infected, and without initial agglutinins, developed O titers to 1:100 or 1:200. These reports of O-agglutinin response in orally vaccinated subjects are interesting, in view of the greater immunologic significance attached to O as compared with H agglutinins. Topley and Wilson¹⁷⁴

have suggested the importance of knowing whether Vi agglutinins can be detected in orally vaccinated subjects.

Finally, Ruge¹⁵⁴ reported in 1932 giving 22 men on 3 successive days *per os* a tablet containing typhoid bacterial lysates. Four weeks later, 8 showed agglutinin titers of 1:400, 8 had no agglutinins, and the remainder showed intermediate titers. Two subcutaneous injections of vaccine were then given, and the average titer for the group rose to between 1:1600 and 1:3200: whereas controls receiving only the 2 subcutaneous inoculations developed an average titer of 1:400 to 1:800. He concluded that oral vaccination might produce a specific preparedness of the tissues, manifested in a more rapid and abundant production of antibodies on subsequent exposure to the same antigen.

Many workers were much less successful. For instance, in 1924 Achard and Bloch¹ detected no agglutinins, but a delayed and irregular development of complement-fixing bodies, in 8 persons who had received orally, along with a cholagogue, 2 cc. of standard T.A.B. vaccine before breakfast on 6 successive days. Similar negative results occurred in 5 women, who swallowed 2 bili-vaccine pills daily for 3 days—double the dose then generally used.

Poor serologic responses were likewise recorded by Rosa,¹⁴⁰ who fed 33 persons 4 T.A.B. tablets on 2 successive days before breakfast. A month later, 1 person showed typhoid agglutinins to a titer of 1:200, and all the others had none. Pfeiffer and Lubinski¹⁵⁵ also fed dried typhoid bacilli to 12 students, and 2 to 6 weeks later found no circulating agglutinins or bacteriolysins. In 1937, Lewin, Gear and Landau¹⁵⁶ published a comparative study of the antibody formation, involving 60 healthy South African natives. One group received subcutaneously 2 doses of typhoid vaccine, with 1 week between doses; another group was similarly treated with Grasset's typhoid "endotoxoid"; and the third group received oral typhoid vaccine in pill form, on 3 successive morn-

ings, a bile pill being given the previous evening. The products were all prepared from the same strain of *Eb. typhosa*. Samples of blood were collected 2 and 4 weeks respectively after the last dose of vaccine, and the sera tested for H and O agglutinins and complement-fixing bodies. A feeble antibody response was shown by the orally vaccinated group. The average O agglutinin titer merely doubled, rising from roughly 1:20 to 1:40, by contrast with an average rise to around 1:400 in persons receiving the antigens subcutaneously.

More recently, Naumer and Nerb¹⁴⁴ gave a commercial preparation of typhoid vaccine orally to 6 individuals, 3 of them children under 12 years of age. A capsule containing 10 billion heat-killed bacilli was taken fasting, without bile, on 3 successive mornings. There were no reactions but only 1 subject showed a slight rise in agglutinin titer. Elledge, Kennedy and Cumming⁶⁸ also reported findings on a large group of adults, 1200 of whom received T.A.B. vaccine subcutaneously, while 850 took it by mouth in capsules, again without bile, on 3 mornings before breakfast. Reactions were commoner among the subcutaneously inoculated, but nausea and "upset stomach" were noted by some who swallowed capsules. Slide agglutination tests carried out on 50 persons in each group showed some agglutinin response among all injected with vaccine, whereas 35 of the orally vaccinated group did not respond, and the remainder had very low titers.

To sum up this section, ingestion of large doses of killed typhoid-paratyphoid bacilli may lead to antibody formation in laboratory animals and man. When antibodies do appear, they are at lower titers than those customarily noted after parenteral inoculations of similar antigens. Apart from conventional antibodies, and any general immunity which these may signify, animal experiments suggest that some degree of local immunity may be induced in the intestinal wall, by ingestion of either living or heat-killed

vaccine; but the adequacy of any protection afforded by these immunity mechanisms appears dubious. Bile may facilitate absorption of some orally administered antigens; but in the small doses employed clinically its effects must differ from those which follow treatment of experimental animals with the large amounts used by Besredka.

Prophylactic Administration of T.A.B. Vaccine Orally to Man. Most of the clinical reports on oral vaccination of man against enteric infection are unsatisfactory since immunization was usually begun in the decline phase of epidemics. Further, where oral and parenteral routes were compared, factors conditioning the choice of route in given individuals could have greatly affected their exposure risks. Only brief outlines will therefore be given of certain outbreaks hitherto adduced as evidence of the efficacy of oral immunization.

Dubarry⁶¹ reported the effects of vaccination in a serious outbreak of typhoid fever among 1000 prisoners of war at Toulouse in 1914. About 6 weeks after the epidemic began, 282 persons received 3 injections of vaccine, while 373 took without ill-effects 2 of Lumière and Chevrotyer enterovaccine pills. During the 1st fortnight after vaccination began, 3 persons receiving the injected vaccine developed typhoid fever. No further cases occurred thereafter. The author naively states that the most energetic prophylactic measures were instituted simultaneously with vaccination.

A number of similar reports appeared in France and South Africa soon after Besredka's work had attracted attention. Vaillant¹⁷⁷ first recorded a large-scale application of the bili-vaccination method to man. In 1921, a group of 6 villages in the war-devastated region of Pas-de-Calais were stricken with a typhoid fever outbreak. The living conditions were very squalid, with bad overcrowding, and contaminated wells. Vaccination was regarded as the sole weapon available against the epidemic; but in view of the general disinclination of the inhabitants

to risk reactions, 1236 received the vaccine orally, and 173 subcutaneously, while 600 to 650 persons remained non-vaccinated. Among the non-vaccinated there were altogether 50 cases of typhoid fever (21 after vaccination had begun in the area); among the subcutaneously vaccinated, 4 cases developed within 5 to 12 days after the last injection; while only 3 cases developed among the orally vaccinated, all within 10 days after ingestion of the vaccine. Although Vaillant found these figures encouraging, he erred in calculating the incidence rate for the non-vaccinated on the basis of total cases since the epidemic began, instead of cases subsequent to commencement of vaccination. When this correction is made, the non-vaccinated case incidence was 3.2%, a figure approaching the 2.3% incidence for the subcutaneously inoculated group. The superficially impressive difference between these rates, and the 0.17% incidence calculated for the orally vaccinated, is statistically insignificant in the face of lack of epidemiologic evidence pointing to equality of exposure in the groups compared. Calmette²⁴ early pointed out that proper assessment of the efficacy of typhoid vaccine taken by mouth would entail carefully controlled experiments over a period of years, involving large numbers of subjects, in areas of typhoid fever endemicity.

The Pas-de-Calais episode was prototype to others to which similar criticisms apply. Besredka¹⁶ himself reported a typhoid epidemic at the military college of La Flèche in 1923. After the peak had passed, 253 students received T.A.B. vaccine subcutaneously, and 268 physically weaker ones took his bili-vaccine by mouth. Among the former group, 10 contracted the disease within 20 days after inoculation; of those vaccinated by mouth, 5 fell ill within 11 days. Besredka regarded this outbreak as comparable to a laboratory experiment, since all the students lived under the same conditions, and concluded that the bili-vaccine was at least as efficacious as T.A.B. vaccine given by injections. However, only 2 sub-

cutaneous inoculations appear to have been given, on successive days, which are not optimal conditions for this method. Moreover, according to Calmette,²⁴ this outbreak was water-borne, and since the suspected water supply was doubtless banned, such cases as occurred thereafter were presumably due to chance encounters with *Eb. typhosa*. The numbers involved at La Flèche were again not large enough to furnish comparable indices of immunity with so inconstant an exposure risk.

Gauthier²⁵ reported, in 1924, his experiences in Greece during the expulsions from Asia Minor, when the value of subcutaneous T.A.B.C. vaccine was incontestably demonstrated on over 650,000 refugees. A limited trial of oral immunization was made on some 1200 non-refugees living in Athens and Salonica. In the ensuing 6 months, no typhoid cases occurred among this group. Also, the inhabitants of villages where typhoid outbreaks had occurred ingested 3 billion polyvalent, heat-killed organisms, without bile, on 3 successive mornings before breakfast. Some 3500 persons in all took the vaccine, and only 5 among them developed typhoid fever.

A large-scale trial of bili-vaccine pills was reported from an oil center town in Rumania by Cantacuzène and Panaitescu²⁶ in 1925. After 54 typhoid cases had occurred, an intensive vaccination program was launched. A total of 8673 received T.A.B. vaccine subcutaneously; 2286 took bili-vaccine by mouth; 5575 controls remained untreated. Of 45 subsequent cases, 3 arose in the inoculated group (0.035%), and 6 in the orally treated (0.26%). Unfortunately, these figures did not include cases among the many persons, vaccinated or not, who left the city during the outbreak.

The poor level of sanitation and of community intelligence among the native populations of South Africa mines and villages led to extensive trials of oral vaccination there. From Pretoria²⁷ it was reported in 1927: "Natives most strongly object to having needles stuck in them.

. . . They raise no objections to taking any amount of medicine by mouth. . . In none of the thousands of natives orally vaccinated has any malaise occurred." In 1923, Pirie and Orenstein¹²⁸ administered orally to about 3500 native employees of a Witwatersrand gold mine, where 35 cases of typhoid fever had broken out, a teaspoonful suspension of 40 billion polyvalent typhoid bacilli, with an ox-bile pill, on 3 successive days. Of 20 subsequent cases, 16 occurred among 3500 vaccinated employees (0.57%), and 4 among 100 non-vaccinated (4%). Boyd²⁹ reported in 1928 that bili-vaccine pills had been given to 2400 Europeans and colored persons in Pretoria, without ill-effects, and with no instance of typhoid fever in persons to whom the pills had been given "within a few days of exposure to infection." Boyd also stated that 14 intestinal carriers of typhoid bacilli had given negative stool cultures following oral vaccination. Cluver⁴² in 1929 wrote even more enthusiastically of the reduced incidence of typhoid fever in various gold mines after oral vaccination. Many of these reports from South Africa are of little significance, since all mines were then under pressure, to which they responded in varying degrees, to improve their sanitation standards. Incidence rates for different years were compared when oral vaccination cannot have been the only variable; and there was occasional evidence of invalid statistical calculations.

The foregoing optimistic claims from the field must be contrasted with the 1931 report of De Mello *et al.*,⁵¹ who found no differences between the typhoid fever incidence shown by orally vaccinated and unvaccinated persons in Portuguese India. Moreover, other reports from South Africa summarized by Lewin,¹⁴⁵ in 1938, were unfavorable to oral immunization. His own statistics showed that oral vaccination failed to reduce the typhoid incidence over a period of several years. Indeed, the annual attack rate of verified typhoid fever in gold mine laborers was actually higher among the orally immunized—

fact ascribed to the greater infection risks faced by the more usually vaccinated underground laborer, as compared with the surface worker. Grasset,⁸⁴ in 1939, stated moreover that the typhoid morbidity and mortality rates in the Rand gold mines during 1934-1936 were 7 times higher among nearly 80,000 immunized employees than among roughly 150,000 who had received his endotoxoid subcutaneously.

BACILLARY DYSENTERY. Shiga's isolation of the causal microorganism of the most severe form of dysentery, in 1898, stimulated interest in the feasibility of vaccination against this disease. Various methods were suggested for reducing the extreme toxicity of even heat-killed cultures, including admixture of the bacilli with immune or normal serum, and vaccination *per os*. Preliminary results in animals were encouraging, but interest faded until reawakened by the work of Besredka, which led to extensive trial of oral immunization against Shiga dysentery in man. The types of experiments conducted closely resembled those described in the foregoing section. The results obtained, and the fallacies inherent in the conclusions often drawn therefrom, were likewise analogous. The relevant literature will therefore be reviewed in less detail.

Results of Animal Experimentation. At the International Congress in Moscow in 1904, Gabritschewski⁷⁶ briefly alluded to animal experimental findings which suggested the possibility of oral immunization of man against acute intestinal infections, such as dysentery, typhoid and cholera. On the same occasion, Zeitlin⁸⁹ reported having himself swallowed 6 doses of heat-killed Shiga bacilli, ranging up to 10 mg. of bacterial bodies, over a 26 day period. There were no ill-effects, and no antibodies developed. Hida and Toyoda⁹⁰ recorded agglutinin and bacteriolysin formation in guinea pigs fed with peptic and tryptic digests of dysentery bacilli, but found no such response to ingestion of heat-killed cultures. Shiga¹⁶⁴ immunized

rabbits by feeding heat-killed cultures of his bacillus. When challenged intravenously with toxin, his animals showed protection against intestinal effects which killed controls in 1 to 2 days, but they died later with spinal paralysis. Shiga also alluded to good results with the vaccine in mental hospital patients.

Chvostek,⁴¹ in 1908, recorded irregular immunity development, unrelated to antibody formation, in rabbits fed with large doses of killed or living Shiga bacilli. Parenteral inoculations proved more effective. Dopter⁵⁸ also showed that mice could be similarly immunized by mouth against 1 to 2 M.L.D. of Shiga bacilli. Excessive doses of vaccine killed the mice, and small doses failed to immunize. Immunity developed only after 10 to 12 days, and did not last beyond 30 days. Later, Dopter⁵⁹ stressed the impracticability of the oral route in man, in view of the large doses needed (15 gm. daily), as judged by the requirements in mice.

In 1910, Dopter and Repaei⁶⁰ noted that the inflammatory and ulcerative changes found post mortem in the large intestine of rabbits given live cultures of Shiga bacilli by mouth, or subcutaneously, were similar to those present in the natural disease of man. Several years later, Besredka¹² reopened study of this question by confirming Dopter and Repaei's findings. He also reported that agglutinins appeared after a single large ingestion of such bacilli; and that rabbits thus treated were vaccinated against living bacilli injected intravenously. In view of the innocuity of the procedure, he urged its trial prophylactically in man. Soon afterwards, Besredka¹⁴ showed that his observations on rabbits applied also to mice. He further noted that rabbits which had developed serum agglutinins after receiving heat-killed Shiga bacilli *per os* soon lost these agglutinins, and could not be stimulated to produce more by additional ingestions of bacilli. Nevertheless, such animals exhibited a solid immunity, which he concluded was entirely localized in the intestinal mucosa, against a severe chal-

lenge dose. According to Besredka, in seeking to provoke such immunity one should avoid production of antibodies, since these are only acquired at the price of severe reactions. Bile facilitated development of immunity, but was not deemed essential here, because the desquamating action prerequisite to absorption of the bacilli was achieved by the organisms themselves.

Kanai,⁹⁵ in 1921, endeavored to reproduce Besredka's results in rabbits, but obtained only slight immunity after oral vaccination. Ingestion of large doses of *Sh. dysenteriae*, living or dead, had no effect upon the health of rabbits. Cultures of enfeebled virulence may have been used. Dumas and Combiesco⁶³ also failed to produce intestinal lesions by feeding live Shiga bacilli to fasting rabbits. However, paralyzes and cecal lesions resulted from giving toxic 8 day culture filtrates by mouth to rabbits and guinea pigs. Half the animals died. The survivors were resistant to 4 M.L.D. of living bacilli injected intravenously. In 1925, Enlows⁶⁹ reported a 57% survival rate in a group of 106 rabbits vaccinated by mouth, and then challenged intravenously, as against 70% in a similar group subcutaneously immunized. Bile was shown to be unnecessary, and possibly disadvantageous, in promoting oral immunization. The oral vaccinating doses contained 100 to 200 times as many heat-killed organisms as were given subcutaneously, but caused fewer fatalities (30% as compared with 43%). Not only do these reports in general dispute many of Besredka's claims regarding the efficacy of immunization by mouth, but Enlows' results indicate the potential dangers of perorally administered Shiga bacilli.

Recently, Cooper and Keller⁴⁴ provoked high degrees of immunity in mice against *Sh. sonnei* by gavage and voluntary drinking. About 300 billion living or killed *Sh. sonnei* given in 4 days induced resistance to 16 to 160,000 M.L.D. of homologous organisms suspended in mucin and injected intraperitoneally. Smaller dosage

gave rise to lesser degrees of immunity. Powell and Jamieson¹³¹ obtained similar results in mice from oral administration of various types of dysentery "endotoxoids," prepared by Grasset's method of adding formalin to repeatedly frozen and thawed bacilli. Endotoxoid derived from 20 billion bacilli given orally twice daily for 5 days proved harmless to mice, and induced immunity against injected challenges of 10 to 100 M.L.D. of culture—a degree of immunity comparable to that noted by others in mice immunized parenterally.

Reports on Administration of Shiga Dysentery Vaccine per Os to Man. In 1922, Nicolle and Conseil^{117,118} presented reports on the successful vaccination of man against Shiga dysentery by Besredka's method. They selected dysentery and brucellosis as suitable infections for experiments in man, on the grounds of their controllability. Since native Tunisians were usually resistant to Shiga dysentery (a fact ascribed to the drinking of polluted waters since infancy), they used subjects of European extraction. Over a 5 day period, 2 volunteers ingested four 100 billion doses of heat-killed Shiga bacilli. Just over 2 weeks later, 1 of the subjects swallowed 10 billion, and the other 20 billion living Shiga bacilli. Both remained perfectly well. Two unvaccinated controls given the same dosages contracted typical dysentery, verified by stool culture. Gauthier⁷⁸ reported in 1924 the results of bacillary dysentery prophylaxis through oral vaccination, carried out in Greece under the auspices of the League of Nations. In all, some 30,000 persons received 3 daily doses of the vaccine, each comprising 3 billion heat-killed Shiga and Flexner bacilli. No cases of dysentery were subsequently reported among the vaccinated. Several examples were cited of epidemics which ceased abruptly and completely after oral vaccination. In a refugee camp of 4000 persons, contaminated well water had given rise to 400 cases of proven Flexner dysentery, with 50 deaths. After two-thirds had received

oral vaccine, dysentery occurred only among the unvaccinated. Another episode involved transferring 340 orally vaccinated refugees from a healthy camp with a good water supply, to another camp with a contaminated supply, where an epidemic was already in progress. None of the migrants developed dysentery.

Less impressive data were offered, also in 1924, by Anglade,³ reporting on a severe dysentery outbreak affecting the garrison and neighboring population in Versailles; and by Antonovsky⁴ describing outbreaks in several Petrograd institutions. Both reports committed the same error of comparing the incidence of dysentery among the orally vaccinated, when the epidemic was past its peak, with the total incidence of cases among the unvaccinated. Moreover, very little bacteriologic work was done. Again in 1924, Pascal¹²² sought to testify in favor of oral immunization by comparing the incidence of Flexner dysentery in an institution whose inmates had not been vaccinated, with the post-vaccinal incidence of Shiga dysentery in the following year.

CHOLERA. Inquiries into the pathology of *V. cholerae* infections in laboratory animals, initiated by Metchnikoff, led to the conception of enterotropism, vigorously sponsored later by Sanarelli. According to Sanarelli, living cholera vibrios administered intraperitoneally to guinea pigs,¹⁵⁶ by mouth or subcutaneously to young¹⁵⁷ and adult¹⁵⁹ rabbits, by the same routes to man,¹⁶⁰ and by mouth to newborn puppies,¹⁵⁸ inevitably made their way to the mucosa of the small intestine. Masaki,¹¹¹ and more recently Solarino,¹⁶⁷ came to similar conclusions. Besredka, less convincingly, ascribed enterotropic properties also to typhoid, paratyphoid and Shiga dysentery bacilli. There are but few reports on oral immunization against cholera; perhaps because the immunity induced by cholera vaccine subcutaneously is too incomplete and transitory, and reactions too slight, to justify risking still more uncertain degrees of

protection against so serious a disease.

Fairbrother⁷⁰ has summarized the various cholera antigens which had been employed parenterally prior to Besredka's work. Until then, the only noteworthy attempt at oral immunization with cholera vaccine was made by Hida and Toyoda,⁹⁰ who fed guinea pigs filtered peptic and tryptic digests of *V. cholerae*. Serum agglutinins and bacteriolysins appeared after 8 to 14 days. The applicability of Besredka's theories and methods to experimental cholera infections in animals was reported by Masaki¹¹¹ in 1922, Glotoff,⁸¹ in 1923, Horowitz-Wlassowa and Pirojnikowa,⁹⁴ in 1926, and by Pfeiffer and Lubinski,¹²⁵ in 1930. Masaki found rabbits and guinea pigs completely refractory to living vibrios taken by mouth. After bile sensitization, rabbits became susceptible to cholera endotoxin, and succumbed in 1 to 2 weeks from repeated ingestions of large doses of living vibrios. Animals surviving a minor cholera infection were able to resist a normally fatal intravenous dose of living vibrios. Masaki concluded that immunity to cholera infection in rabbits and guinea pigs is localized in the intestine. Glotoff, working mostly with rabbits, and Horowitz-Wlassowa and Pirojnikowa, using guinea pigs, recorded essentially similar results and conclusions. Pfeiffer and Lubinski fed rabbits heat-killed cultures of *V. cholerae*. Serum bacteriolysins appeared, but agglutinins only developed in bile-treated animals.

Calmette²⁴ expressed doubt whether oral vaccination against cholera in man would be feasible, but alluded to trials of the method then being conducted in Russia. Such brief reports as have been available from that country and elsewhere seem too unconvincing and contradictory to require mention.

TUBERCULOSIS. Calmette and Guérin,²⁵ in 1906, contended the pathogenesis of tuberculous infection in man and animals involved passage of the bacilli through buccal and intestinal mucous membranes to the mesenteric ganglia. From here,

bacilli might be carried by the lymphatic circulation into the right heart, and thence to the lungs. According to them, even pulmonary tuberculosis was intestinal in origin rather than droplet-borne. This view, which was propagated by these workers for many years, led them to investigate the immunizing efficacy of avirulent tubercle bacilli when given by mouth to young animals. Preliminary experiments on calves and kids, with a heat-attenuated human strain, were sufficiently encouraging to evoke the prediction that so inoffensive a mode of vaccination might be applied to infants.

In 1920, Calmette and Guérin²⁹ reported that an initially virulent bovine strain of *M. tuberculosis*, first isolated by them 12 years before had become so avirulent that at least 44,000 bacilli could be safely given intravenously to man. By 1924, the strain had become completely avirulent for all animal species, and a vaccine prepared from it had rendered young calves resistant to large doses of virulent bacilli.³⁰ Calmette, Boquet and Nègre³¹ soon afterwards showed that young rabbits and guinea pigs could be successfully vaccinated against experimental tuberculosis by repeated oral administration of B.C.G.; and in 1925 Wilbert³² reported that chimpanzees and other anthropoids could be similarly protected against infection from apes with which they were cohabiting.

In 1928, Calmette *et al.*³¹ published figures showing the apparent prophylactic value of B.C.G. given orally during early infancy. The merits and limitations of the immunity conferred on humans by B.C.G. vaccine are still controversial, and it is obviously difficult to assess the relative efficiency of a given route of administration as long as the actuality of immunization by any route remains in dispute. Among the multitude of papers published on B.C.G. in recent years, it is impossible to be confident of selecting the most authoritative. However, 2 impressions are outstanding: (1) that the evidence favoring B.C.G. is making converts at a quickening pace; and (2) that

the oral route is mostly being abandoned. There are exceptions to this trend. De Assis,⁵⁰ reviewing 17 years' experience with B.C.G. vaccine in Brazil, reported good results, with certain provisos, from the oral route. Again, Gomez Ullate⁵³ has commended from Spain the simplicity, economy and effectiveness of the oral route, and advocates routine vaccination at birth, with revaccination by the same route at 1 and 3 years of age, and subsequently on changes of environment. On the other hand, Cantonnet Blanch *et al.*⁴⁰ repudiated the oral route as giving unsatisfactory results in Uruguay. They ascribed this to frequent rejection of the vaccine through vomiting. A recent British review¹¹² summarized the problem thus: "Statistical data derived from oral vaccination of the newborn are unsatisfactory because of uncertainty of B.C.G. infection, lack of control, and difficulty of separating specific from non-specific factors. But there can be little doubt that the vaccinated groups—perhaps 2 to 3 million in all—have shown a decidedly lower mortality from tuberculosis during childhood years than non-vaccinated infants in the same communities."

THE BACTERIAL EXOTOXINS ABSORBED THROUGH THE ENTERON. Two important bacterial exotoxins share the property of exerting specific effects upon the central nervous system after absorption from the enteron. These are the toxins of *Cl. botulinum*, and the enterotoxin produced by some strains of staphylococcus. A few references will also be made in this section to the immunizing efficacy of scarlet fever toxin, and of diphtheria toxin, when taken by mouth.

As long ago as 1891, Ehrlich⁶⁷ reported that mice could be immunized *per os* against as many as 200 to 800 M.L.D. of the plant toxin *ricin*. Their blood serum showed specific antitoxic properties. Ehrlich's findings, confirmed in 1937 by Allin,² suggested that some bacterial toxins might resist destruction by the gastro-intestinal enzymes, and exercise some antigenic effect after absorption.

Tetanus and diphtheria toxins, and snake venom, were found to be largely destroyed in the upper part of the alimentary canal. The discovery by van Ermengen, in 1897, of the causal bacillus of botulism, and Barber's demonstration, in 1914, that staphylococcal growth products might cause gastro-intestinal disturbances when swallowed by man, furnished examples of bacterial toxins apparently unaffected by the digestive juices.

Botulinum Toxin. Tchitchkine¹⁷⁰ attempted, in 1905, to immunize rabbits by mouth against botulinum toxin, but produced only a slight degree of active immunity, while their serum acquired no protective power. Tani¹⁶⁸ reported, in 1934, that several doses of a formalinized toxin given daily to guinea pigs produced circulating antitoxin. However, animals receiving identical dosages subcutaneously developed a much higher antitoxic titer. Recent work in this laboratory by Wood¹⁸⁵ showed negligible immunity development in mice given Type A botulinum toxoid intensively by mouth.

Staphylococcus Enterotoxin. Barber⁹ noted that farm residents who had frequently consumed milk from a cow excreting staphylococci from the udder were resistant to gastro-intestinal disturbances suffered by visitors who drank the same cow's milk. In 1931, Dack, Jordan and Woolpert⁴⁹ found that subminimal reacting doses of filtrate from a food poisoning strain of staphylococcus, given orally to volunteers almost daily for several weeks, provoked little or no immunity. Dolman⁵⁵ reported, in 1943, that subjects reacting violently to enterotoxin on multiple occasions over several months, showed no evidence of acquired immunity. These findings were later extended.⁵⁶ Volunteers who had retained an unaltered susceptibility to ingested enterotoxin became refractory for several months to at least 5 minimal reacting doses after a series of subcutaneous injections of enterotoxin.

Scarlet Fever Toxin. Dick and Diek⁵² noted the inefficiency of oral immunization with scarlet fever toxin. To 19

Dick-positive children, they gave *per os* 12 to 16 daily doses, increasing from 4 to 16 cc. of undiluted toxin. For comparison, some 200 susceptibles received the customary series of 5 graduated doses subcutaneously. Among those treated orally, 73% were Dick-negative after an average total of nearly $8\frac{1}{2}$ million S.T.D.; while of those inoculated subcutaneously with a total of 135,500 S.T.D. each, 93% showed a negative reaction. Later,⁵³ they employed coated tablets containing concentrated toxin in amounts up to 2 million S.T.D. per tablet. These were fed to 131 susceptibles, ranging in age from 1 to 36 years, who were skin-tested before and after the series had been taken. In a group of 102 persons, 95% were Dick-negative 2 weeks after the last dose. It was recommended that a total of 75 million S.T.D. should be taken within 3 weeks. Searlatinal rashes, vomiting and diarrhea often occurred when the tablets disintegrated in the stomach. Carefully prepared tablets only occasionally caused cramps and transient rashes.

Diphtheria Toxin. Chvostek⁴¹ fed diphtheria toxin to 10 guinea pigs, but only 1 survived subcutaneous challenge with 2 M.L.D. of toxin. On the other hand, Breton and Petit²¹ fed guinea pigs cultures of *C. diphtheriae*, attenuated or killed by heat, and the animals later withstood inoculation of more than 2 M.L.D. of toxin. The inconsistencies apparent between these 2 reports are resolvable by assuming that small amounts of diphtheria toxin, adsorbed on bacterial bodies, might survive contact with intestinal enzymes, and cause a slight production of antitoxin. Dumas, Combiesco and Baltiano⁶⁴ killed guinea pigs and rabbits by oral administration of very large doses of diphtheria toxin.

Bousfield¹⁹ reported, in 1945, that increased circulating antitoxin developed in humans who had sucked pastilles containing diphtheria toxoid. The method was ineffective as a primary immunization stimulus. He thought at least 3 pastilles, of 100 Lf content, should be sucked daily

for 1 week if a marked rise in antitoxin titer were sought. Four subjects who swallowed gelatin capsules containing the equivalent amounts of toxoid showed no increased antitoxin. The antigenic stimuli were therefore held to take place between the lips and the lower end of the esophagus, rather than through the gastro-intestinal mucosa.

THE MISCELLANEOUS MICROORGANISMS.
Pasteurella Pestis. Fornario⁷⁵ claimed that heat-attenuated plague bacilli, given in 2 doses *per os* or *per rectum* at 10 to 14 days interval, incited immunity to subcutaneous challenge with virulent cultures in two-thirds of a small group of rabbits and guinea pigs. Serum antibodies, notably opsonins, also appeared. Noe¹¹⁹ and also Leger and Baury¹⁰³ recorded inconclusive experiments of a similar nature.

Pseudomonas Aeruginosa. Courmont and Rochaix¹⁷ administered heat-killed, 8 day broth cultures of *Ps. aeruginosa* (*Bacillus pyocyaneus*) to rabbits by rectal instillation. Three doses of 100 cc., given with a long cannula, at 5 day intervals, were well tolerated. One month after the last dose, the animals were challenged intravenously with virulent homologous culture. They developed fever, diuresis and loose stools, but recovered after a few hours. Controls died.

The Brucella Group. Nicolle and Conseil^{117, 118} gave 2 volunteers *per os* within 5 days a series of 4 doses of 100 billion killed *Br. melitensis*. A fortnight after the last dose they had no detectable agglutinins. Challenged subcutaneously with live culture, they remained well, whereas a similarly inoculated control subject became ill 17 days later, with verified brucellosis.

Dolman and Hudson⁷⁷ reported that 4.5% of over 5000 blood specimens from inhabitants of an area where Bang's disease was prevalent completely agglutinated brucella suspensions in a titer of 1:20 or higher. Since most of these specimens came from persons with no history of brucellosis, the agglutinins presumably developed as a result of frequently re-

peated ingestions of dead or living *Br. abortus*. An unpublished experiment involving 2 volunteers showed that a single, large dose of killed *Br. abortus*, taken in milk, resulted in no increased titer of serum agglutinins.

Exclusively Non-human Animal Pathogens. Gaiger⁷⁷ reported, in 1909, that young buffaloes which had repeatedly drunk large doses of *hemorrhagic septicemia* bacilli survived a normally fatal subcutaneous challenge with virulent culture. The immunity was incomplete and transitory, but was held to explain the natural resistance to infection shown by old animals in endemic areas. Baldrey⁸ carried these inquiries further, and confirmed Gaiger's claims. Since 1 out of 14 bulls died of infection from the oral vaccination, the procedure was not regarded as safe.

Baldrey also attempted unsuccessfully to vaccinate 12 bulls against *rinderpest* by administering with their food or water 2 small doses of blood from infected animals. Calmette²⁵ later quoted Van Saecghem as claiming successful protection following a single ingestion of fecal suspension, prepared from an artificially infected animal treated with antiserum. These references to *rinderpest*, and a curious observation by Repetto¹³¹ that rats and mice fed normal nervous tissue became resistant to subcutaneous injection of *rabies* street virus, exemplify the paucity of the literature on oral immunization against virus infections.

Duff⁷² showed that trout developed immunity to *fish furunculosis* after repeated feedings (64 or more) with hatchery food containing the causal pathogen, *Bacterium salmonicida*. Specific agglutinins developed in many of the vaccinated fish, and when exposed to infection their mortality was 25% against 75% for untreated fish.

THE PROGENIC COCCI. These microorganisms have certain common features, apart from morphology, to justify their being grouped together in this final section. The alimentary canal seldom serves as their portal of entry into the host; the defence mechanisms against them appear

mainly phagocytic; and they frequently become secondary invaders, especially in respiratory tract infections.

Staphylococcus. Calmette and Petit⁸² showed, in 1907, that virulent staphylococci administered to rabbits by stomach tube, soon appeared in the blood stream and killed the animal within 24 hours. Given rectally, the sequence of events was slower. Osteomyelitis appeared either spontaneously, or after trauma. Courmont and Rochaix⁴⁸ could incite only partial immunity in rabbits by rectal instillations of *Staphylococcus pyogenes aureus*. Combiesco and Calalb⁴³ also tried unsuccessfully to immunize rabbits orally, with or without use of bile, against intravenous challenges with staphylococci. Winzeler¹⁸³ reported better results in guinea pigs given many large doses of staphylococci by stomach catheter. A majority of animals fed living organisms later survived challenge with 3 M.L.D. of culture, but the killed organisms provoked inferior degrees of immunity. Coincident use of bile did not improve the immunity acquired.

Streptococcus. Tchitchikine¹⁷¹ reported rabbits frequently died of streptococcal septicemia when fed live cultures, but took heat-killed cultures with impunity. Rabbits surviving such ingestions showed no acquired immunity against challenge 6 months later with living organisms. Winzeler¹⁸³ fed guinea pigs large doses of *Strep. haemolyticus*, living and dead, without significant immunity development. Kolmer and Amano⁹⁷ also failed to immunize rabbits against intracisternally injected virulent streptococci, despite 30 daily ingestions of 5 to 10 cc. of culture, living or heat-killed. Moreover, no agglutinins developed.

Pneumococcus. The oral immunization against pneumococci has yielded more impressive results. In 1927, Kimura⁹⁶ fed many large doses of heat-killed Type I pneumococci to mice, and found 5 out of 8 withstood 100 M.L.D. of injected live culture. Kolmer and Amano,⁹⁷ in 1932, reported irregularly immunity development in rabbits following 30 daily admin-

istrations of heavy doses of pneumococci by stomach tube. Some animals survived intratympanic injection of homologous culture in amounts fatal to controls. The best protective results were obtained from ingestion of living Type I pneumococci. The authors ascribed the comparative rarity of pneumococcal meningitis in human paranasal sinus infections to immunity derived from continually swallowed organisms.

Meanwhile, in 1926, Ross¹⁴⁴ published the first of several important papers on oral immunization against pneumococci. He used white rats in his experiments, since mice responded irregularly, and rabbits negatively. Rats fed repeatedly on tissues from rats which had died of Type I pneumococcus infection survived intraperitoneal challenge with 1000 to 10,000 M.L.D. of homologous organisms. It was suggested that these findings might account for the infrequency of lobar pneumonia from pneumococcus types commonly present in normal throats. Almost equally good results were reported by Ross¹⁴² from repeated feedings with living Type I pneumococci. Equivalent dosages of heat-killed organisms, or of culture filtrates, were ineffective, but hydrochloric acid-killed organisms¹⁴⁴ gave good protection. Ross¹⁶⁰ also showed immunity thus acquired was of variable, but on the whole brief duration, many large ingestions of preferably living organisms being needed to procure its persistence for 1 to 2 months; occasionally up to 4 months.¹⁴³ But lapsed immunity could be restored by a single feeding. Pneumococci desiccated after mechanical disruption, or dissolved in bile salts,¹⁴⁵ and also Type I specific soluble substance,¹⁴⁷ produced almost equally good protection when fed to rats.

Ross^{146, 148} soon extended his observations to cover Types II and III pneumococcus. He also showed¹⁴⁹ that most of the soluble specific substance ingested by rats was excreted unaltered in the feces. He concluded tentatively that certain cells of the gastro-intestinal tract were

responsible for their increased resistance. However, in 1934, he¹⁵¹ reported the presence of protective antibodies (against pneumococci given intraperitoneally to mice) in the blood of rats orally immunized against Type I pneumococcus, and suggested positive protective antibody tests in human sera might indicate increased resistance. Similar protective antibodies were detected¹⁵¹ in rats fed with Types II, III and IV. Finally, he¹⁵³ detailed the results of feeding 63 individuals with mixed Types I, II and III preparations. Within 2 to 3 days after 6 heavy feedings, about 75% of the group formed protective antibodies against Type I, and about 60% against Types II and III. Agglutinins were not detected in these or preceding experiments. Since the antibody level reached (1 cc. of serum protecting a mouse against 5000 M.L.D. of homologous pneumococci) approximated that reported in sera from pneumonia convalescents, its attainment seemed to indicate a generalized specific resistance.

HETEROPHIL AND COMMON COLD ANTIGENS. In 1925, Powell¹²⁹ reported that heterophil (Forssman) antigen administered by mouth to rabbits, in such forms as hen, sheep or goat red cells, evoked high titers of heterophil antibody (anti-sheep hemolysin). Bailey and Shorb,⁷ in 1931, demonstrated circulating heterophil antibody in rabbits fed intensively with heat-killed Type I pneumococci, but higher titers followed a single intravenous injection. These animals were also immune to inoculations of living pneumococci. Rockwell, Van Kirk and Powell¹³⁷ asserted, in 1935, that heterophil antibodies were "effective" against all pneumococcal types, as well as certain streptococcal strains, and several other common secondary invaders in colds. Having noted raised titers of heterophil antibodies in the blood of convalescents from acute colds, they deduced that a "non-type-specific heterophil active immunity" against colds might be provoked by oral vaccination. A capsule of 100 billion heat-killed pneumococci and streptococci

was taken on 7 successive days, and thereafter once weekly throughout the season, by 500 patients. Fewer colds than usual were experienced by this group; but as was pointed out,⁶⁵ the control group was largely invalidated by inclusion of persons with a lower average susceptibility. These authors further stated contradictorily that "bile destroys the heterophil antigen," and that "the vaccine was high in bile-resisting heterophil antigen." Later,¹³⁵ other common respiratory tract organisms were added to the vaccine, with even more favorable results.

Rockwell and Van Kirk^{135,136} sought to correlate heterophil antibody in orally vaccinated subjects with acquired immunity to colds; but their protocols did not indicate prevaccinal titers, although a brief reference in the earlier paper suggests as wide a range of antibody in unvaccinated persons, as was subsequently found in those who took the vaccine. Powell¹³⁰ even developed a serologic method for assaying the adsorbing power for heterophil antibody of mixed cold vaccines. He also applied to such vaccines the method described by Ross¹⁵¹ for determining the protective power of the serum of rats fed with Type I pneumococcal preparations. Thus, although provocation of non-type-specific immunity in humans had been previously urged, a test for cold vaccine was now recommended which measured only type-specific immunity developed by rats.

Working along somewhat different lines, Thomson *et al.*¹⁷³ administered orally to a few volunteers phenol-killed cultures of *H. influenzae* grown symbiotically with *Anaeromyces bronchitica*. Quite marked reactions ensued, and some serum agglutinins and mouse-protecting substances developed. They deduced that a combined vaccine, including pneumococci, streptococci, and *N. calarrhalis*, also grown symbiotically, would have even greater prophylactic value against complication of colds and influenza. The authors kept up their own agglutinins by swallowing a weekly dose of mixed vaccine.

Numerous proprietary preparations of semisecret composition continue to be advocated here and there for oral immunization against ailments ranging from intestinal disorders to rheumatism and coryza. The best that can be said of these is that they pay tribute to the faded prestige of Besredka's doctrines or demand faith in the dubious significance of heterophil antigens.

Discussion and Conclusions. "I had satisfied myself long ago . . . that, though typhoid vaccine may be absorbed by way of the intestinal canal, it is only badly and incompletely absorbed, and above all that its action is uncertain. . . . I do not think it is necessary to go any further than that, for science never sanctions a more complicated and more uncertain method being employed where a simple and certain one, such as subcutaneous inoculation, is available. And I would submit that the idea that a *via media* can be found between the antique system of prescriptions, with doses taken t.i.d. before or after meals, and scientific applications of bacteriology, and the idea that that *via media* can be found in the administration of vaccines by mouth, ought steadily to be put away from us." Thus spoke Wright,¹⁸⁷ pioneer of vaccine therapy, in 1910. Over 30 years later, his long-time associate, Fleming,⁷³ found little cause to modify this opinion, and dismissed the issue in less peremptory but briefer terms: "In certain communities this method has been very popular owing to the ease of administration. Extensive observations have shown that in the enteric group of diseases some immunity can be established by the oral administration of vaccine, but it is not the best method."

Although a review of the literature has shown how aptly and fairly these 2 quotations summarize the status of oral immunization today, the matter cannot be left just there. For even if the inferiority of this route has always been recognized by the prescient and the experienced, its potentialities apparently remain enticing

enough to secure a perennial, sporadic interest. There seems no need to recapitulate the flimsiness of the experimental and epidemiologic supports upon which the protagonists of oral immunization lean. But certain questions remain to be answered. First, what is the likelihood of methods being devised for evoking more predictable and higher immunity responses to orally administered antigens? Secondly, is there a type of local, intestinal immunity, independent of conventional antibodies, which in some circumstances it is desirable, and even preferable, to provoke? Thirdly, are there certain overriding advantages of the oral route—simplicity, cheapness and innocuity, for instance—which, despite inefficiencies, occasionally warrant its adoption? These questions will be dealt with in order.

1. **FEASIBILITY OF INDUCING MORE SATISFACTORY RESPONSES TO ORAL ANTIGEN.** Once swallowed, antigens become subject to successive hazards to their integrity, and handicaps to their absorption. Before any intimate contact with the intestinal mucosa is achieved, the antigen faces exposure to hydrochloric acid and pepsin; to bile, trypsin, and other proteolytic enzymes of intestinal or even bacterial origin—all liable to be encountered in concentrations and at intervals governed by such variables as the subject's diet, bowel motility, and emotional and physical health, as well as perhaps the state of the weather. Covering the tract is a layer of mucus which presents simultaneously a mechanical barrier, and a menstruum in which leukocytes can better pursue and engulf entangled microorganisms. Goldsworthy and Florey,⁸² and Florey,⁷⁴ have discussed other antibacterial properties of this intestinal mucus.

Antigens surviving these preliminary obstacles impinge upon a mucous membrane of high selectivity, whose underlying mechanism eludes analysis. Considerations of size, motility, or lability cannot wholly account for the different capacities to enter the blood stream shown

by *Eb. typhosa* and other members of the salmonella species; nor for the remarkable discrimination exemplified in human susceptibility to ingested botulinus toxin of Types A, B and E only; and in the innocuity of staphylococcus alpha-toxin⁶⁴ and beta-toxin⁶⁵ taken by mouth, in contrast to the effects of the enterotoxin. The total effect of all these characteristics is to ensure that persons of normal health and habits seldom or never absorb more than trivial amounts of unaltered antigen. This concept readily accounts for the frequent lack of circulating antibody after ingestion of antigen.

However, the impermeability of the intestinal mucosa to proteins is by no means complete. For instance, Makaroff¹¹⁰ induced specific anaphylactic states in guinea pigs by repeated heavy feedings with protein; Hektoen, Kanai and Dragstedt⁶⁹ used precipitin tests to demonstrate absorption of thyroglobulin in dogs fed on beef thyroid; and the Seegals¹⁶³ provoked sterile inflammation in the actively sensitized rabbit eye by introducing homologous antigen into the stomach. Arnold⁶ found that when typhoid, coliform and other bacilli were injected with egg-white into the duodenum of dogs, they passed freely into the thoracic duct, and reached the liver and mesenteric lymph nodes in large numbers. These observations on dogs were extended^{115,166} to cover absorption of various microorganisms introduced by mouth, intraduodenally or rectally. Fischer^{71a,72} also reported that yeast administered orally and rectally was absorbed into the portal circulation.

In 1927, Walzer¹⁷⁸ showed by means of the Prausnitz-Küstner reaction that some fish and egg protein taken by man in physiologic amounts was customarily absorbed undigested. Ratner and Gruhl¹³³ reported similar observations, and suggested that protein absorption in man might usefully serve the purpose of keeping the body immunized against habitual protein diets. Arnold, viewing the fore-

going findings from another standpoint, contended⁵ that alterations in permeability of the enteron occurred naturally in response to various environmental stimuli, and might be correlated with certain epidemiologic phenomena. Later⁶ he stated: "The intestinal mucosa is . . . a permeable body covering and the reticulo-endothelial network within the splanchnic region is the real barrier against systemic invasion." Alluding to experiments by Peterson, Müller and Boikan,¹²⁴ in which marked splanchnic reactions were the first tangible effects of continuous intravenous perfusion of dogs with *E. coli*, Arnold urged that specific immunity might be simply and physiologically acquired by applying splanchnic stimuli, after orally administered antigen had passed the enteron and was fixed in the splanchnic reticulo-endothelial system. The evocation of these stimuli would certainly provide a fertile field for necromantics.

Proofs of protein absorption explain the many reports of irregular antibody production following ingestion of antigen. They account also for such observations as those of Tenbroeck¹⁷² on specific antitoxin in the blood of intestinal carriers of *Cl. tetani*. Furthermore, they strike at the very roots of Besredka's doctrines, that the host's sole defence against bacterial invasion from the enteron was an intact gastro-intestinal mucosa, which could be rendered impregnable by assimilation of "antivirus," a soluble component released from ingested bacteria by phagocytosis. But oral immunization now faces multiplied theoretical difficulties; for the destiny of that variable portion of ingested antigen which may traverse the mucosa, is largely indeterminate. Most particulate elements, mainly transported by leukocytes and macrophages, will reach the mesenteric lymph glands; and the remainder, along with soluble components, will go to the liver directly. The work of Ehrlich, Harris and co-workers^{66,86*} on the rôle of the lymphocyte in immunity, indi-

* For the fate of particulate antigens in relation to antibody formation, see Harris, T. N., and Ehrlich, W. E.: *J. Exp. Med.*, 84, 157, 1946.

cates that any ingested antigens arriving intact in the splanchnic lymph glands might thence call forth efficient antibody responses. The relatively good results from oral B.C.G. vaccination perhaps derive from the high proportion of unaltered antigen reaching this area. As for the liver, despite its importance to immunity in bacteremic conditions,³⁸ its detoxifying functions must also be reckoned with; under the circumstances in question, any large contribution of antibody from that organ could hardly be anticipated. The fate of an antigen, and the kinetics of antibody formation, have recently been studied by a promising new technique, involving the injection into mice of purified tobacco mosaic virus, tagged with radiophosphorus.^{107,155} Application of such methods to ingested antigens should prove illuminating. Meanwhile the assumption seems warranted that oral dosages large enough to ensure regular passage of effective amounts through the intestinal mucosa into the splanchnic depôts, apart from their inconvenience, would entail a heavy risk of overflowing the splanchnic barrier into the systemic circulation, with possible reactions of great severity. Calmette and Breton²⁷ forewarned against such dangers long ago, with respect to tubercle bacilli.

2. SIGNIFICANCE OF LOCAL INTESTINAL IMMUNITY. The largely unconfirmed nature of Besredka's laboratory results, and the doubtful efficacy of his bili-vaccines in man, illustrated earlier in this review, seem inevitable in the light of the foregoing considerations. Indeed, the more extreme and dogmatic aspect of his local immunity doctrines were soon rejected by the orthodox. But there has remained a sufficient afterglow of enthusiasm to inspire the occasional neophyte, or to tempt the uncritical manufacturer; their discouragement seems in the public interest. Hence certain other fallacies should be briefly exposed here.

First, a few comments on the use of bile, whose toxic effects in Besredkan dosages have already been described.

Not only are breaches in the intestinal mucosa unnecessary for passage of antigen, they need not even facilitate this process. Gaiger⁷⁷ failed to induce hemorrhagic septicemia in young buffaloes fed contaminated grass so coarse that stomach abrasions were bound to result; Boone *et al.* (*Proc. Soc. Exp. Biol. and Med.*, 29, 113, 1931) noted no increased absorption of bacteria after injuring the duodenal mucosa. On the other hand, several workers have reported increased permeability of the gastro-intestinal walls after subjecting them to pH changes such as might result from the cholagogue effects of bile. Again, *E. coli* was noted¹¹⁶ in the mesenteric lymph nodes and liver of dogs soon after intragastric administration of saponin, which has a similar effect to bile on surface tension. In the small doses advocated for promoting oral immunization in man, any action of bile is obscure, but may relate to the acceleration of stomach evacuation described by Pannett and Wilson¹²¹ in 1921.

Secondly, the enterotropic concept, which loomed large in Besredka's writings, is a relative, teleologic term. Harvey⁸⁸ referred to a septicemic type of typhoid fever, without intestinal symptoms, in which the tonsils and throat served as portal of entry. Even complete intestinal immunity could furnish no protection here. Benians¹⁰ reported that in experimental coli-typhoid septicemias, the organisms migrated into subcutaneous fixation abscesses induced by gum tragacanth, this suggesting a possible "mucotropism" rather than any selective organ affinity. Besides, no matter how large the dose of vaccine ingested, it is hard to conceive that all the innumerable crypts and tortuosities of the gastro-intestinal mucosa could thereby be rendered impervious to subsequent infection. On the other hand, it is clearly irrelevant to attempt vaccination of the entire enteron, with a view to securing impenetrability, against organisms whose elective affinities appear to be directed, for instance, towards the respiratory tract, and whose portal of

entry usually lies therein. Only some measure of general immunity could be expected to cope with such contingencies as the foregoing; and the oral route provides only the vaguest assurance of its attainment.

The question remains whether local, intestinal immunity should be sought, either as manifesting an essentially different form of protection, or as providing a supplementary depôt for storage and mobilization of antibodies. Besredka's disparagement of antibodies stemmed mainly from observing that orally vaccinated animals sometimes showed firm protection despite absence of circulating agglutinins, and from instances of immunity having failed in man despite the presence of antibodies. His views served the useful purpose of activating controversy and inquiry respecting the rôle of antibodies, but the evidence is now overwhelming that he erred in denying their significance. According to current immunologic concepts, antibody globulin is believed to be synthesized within such cells as macrophages and lymphocytes adjacent to the site of deposition of antigen.^{33,36} Antibody and serum globulin production are subject to similar limiting influences,³⁷ and their molecules exhibit the same life span.¹⁶¹ The gist of these views may be cogently applied to the present argument, in the following words of Cannon:³⁵ "It is not the fact of antibody concentration in the blood stream at any particular moment that is so significant in resistance as that there has been a retention of the capacity of the antibody producing tissue to become reactivated and thereby enabled to resist bacterial agents against which they have once been immunized." This reactivation process, or anamnestic response, may be extremely prompt, and has been discussed at length by Cannon.³⁴ Mention should also be made here of Wright's impressive recantation,¹⁸⁸ in 1942, of former views on the dependence of the phagocytic activity of leukocytes upon serum opsonins; and of his conviction that phagocytosis may be rapidly stimulated, even *in vitro*, by

vaccination. In sum, although Besredka's local immunity concept found early support⁸⁰ outside discipular circles, modern views on immunity mechanisms point to the probability that the phenomena he observed were at least partly due to antibody globulin held mainly intracellularly, and partly to enhanced phagocytosis. This hypothesis is supported by such observations as those of Torikata and Inaizumi¹⁷⁵ that guinea-pigs fed on *E. coli* or staphylococcus had for a short period higher opsonin titers in fluid extracts of their intestinal mucosa than in their blood serum, while the reverse was true in animals subcutaneously immunized. Favilli and McLean,⁷¹ on the other hand, went so far as to ascribe the major features of local immunity, at least as noted in the skin, to a reduction in the tissue permeability associated with early inflammatory changes, rather than to any specific immune response.

3. *No Present Justification for Even Occasional Resort to Oral Immunization.* The only hypothetical advantages accruing from oral immunization then appear to derive from a temporary and uncertain concentration of antibody, unreleased from cells in the intestinal wall, and in their residual anamnestic potentialities. But such protective mechanisms could only be exercised against agents seeking entry by the alimentary canal. Moreover, the protection would be unevenly distributed, so that through some portal in the long defence line the invader might pass unchallenged, and emerge into relatively defenceless territory. Following parenteral vaccination, a much more uniform and widespread distribution of antibody is brought about by the blood stream.

As an alternative to sole reliance upon oral immunization, the findings of Ruge¹⁵⁴ suggested its supplementation by subcutaneous inoculations. But no benefits would be thus conferred that are not forthcoming, with far greater certitude, from growing acceptance of the need for for an initial series of injections, with "booster" or "recall" stimuli similarly

administered. Fast-improving public attitudes towards hypodermic inoculations should encourage endeavors to reduce the toxicity, and fortify the antigenicity, of products, and to determine how the immunizing capacity of the skin¹⁷⁶ can be used to best advantage. These efforts should not be undermined by any pandering to dim apprehensions, or confused by dissemination of quasi-scientific literature whose esoteric jargon the average practis-

ing physician cannot follow, let alone the layman; and which often enough relates to products incapable, however administered, of conferring specific protection. Unless and until some entirely unforeseen immunologic principles be established, licensing authorities should accept the responsibility of discountenancing distribution of products intended for oral immunization.

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PHYSIOLOGY

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The Blood Pressure of Rats Subjected to Auditory Stimulation. ELEANOR H. YEAKEL, PH.D., and HENRY A. SHENKIN, M.D., with assistance from S. M. McCANN and A. B. ROTHBALLER (Dept. of Research Surgery, Univ. of Penna. and Wistar Institute). After a years exposure to the sound of a blast of compressed air, 5 minutes daily for 5 days a week, the average systolic blood pressure (determined with a tail plethysmograph) of 25 gray Norway rats rose from an initial value of 113 to 154 mm. in the last 2 months. In 17 control animals, an increase from 124 to 127 mm. for the group was found over the same period. Sixteen of the air-blasted rats (64%) and 2 of the controls (12%) had mean blood pressures of 150 mm. or more at the close of the experiment.

Monthly averages indicated that the rise in blood pressure of the experimental rats tended to occur in the 9th month after air blasting was begun. The average of all readings for each rat before and after the rise in its blood pressure showed a mean change of +29 mm. for the group.

Direct measurements of the blood pressure with a Hamilton optical manometer,* made on 11 of the control and 13 of the experimental rats, did not agree with plethysmograph readings on the intact unanesthetized animals. In general, the systolic pressure of the air-blasted rats was lower. When the 2 methods were used on the same animal under ether, the systolic readings agreed closely. In experimental rats, the average diastolic pressure was 89 mm., as compared with 78 mm. for the controls; and values of 90 mm. or more were recorded for 8 of

the former and 1 of the latter. The differences are significant statistically.

The results suggest that the auditory stimulus increased peripheral resistance and raised systolic and diastolic pressure.

Quantitative Measurement of Regional Circulation by the Clearance of Radioactive Sodium. SEYMOUR S. KETY, M.D. (Dept. of Pharmacology, Univ. of Penna. and Metabolic Service, Phila. General Hosp.) A freely diffusible substance injected into a tissue will be carried away from the site of injection at a rate largely determined by the local circulation. If the substance be the radioactive isotope of sodium (Na^{24}), the quantity remaining in the tissue and hence the clearance rate can readily be measured continuously by means of a shielded Geiger-Mueller counter at a fixed distance from the injection site. It was mathematically predicted and experimentally found that the locally injected sodium-disappears along an exponential curve: $Q = Q_0 e^{-kt}$, where Q = quantity of sodium remaining at time, t , Q_0 = initial quantity of sodium injected, k = the tissue clearance constant. This constant is readily obtained as the slope of the straight line which results when Q (in counts per minute) is plotted semi-logarithmically against time. It is further demonstrable that k bears the following relationship to blood flow: $k = \frac{F}{S} \theta$, F = tissue blood flow as cc. per gm. per min., S = sodium space of the tissue as cc. per gm. θ , numerically somewhat less than unity = an overall diffusion factor depending on diffusion distances, capil-

* We are indebted to William A. Jeffers, M.D., of the University Hospital, for performing the determinations.

lary interface, fluid filtration and absorption. Thus the clearance constant, although not a rigid measure of total blood flow, is an accurate and quantitative measure of the effectiveness of the local circulation including not only blood flow but other mechanisms responsible for local homeostasis. In tissues where diffusion occurs rapidly and is not a limiting factor, the clearance constant approximates the blood flow. This technique was employed to study the circulation in the human gastrocnemius muscle. There was satisfactory agreement among values obtained in different subjects. A tourniquet about the thigh invariably brought the clearance constant to zero or practically zero. Reactive hyperemia, exercise and locally injected mechohyl produced a marked increase in the clearance constant, while local administration of epinephrine slowed the clearance markedly. Values for flow calculated from the clearance constants are in general agreement with other estimates for muscle blood flow in man. The convenience of this technique and its ability to yield quantitative values for effective circulation may make it a useful clinical method.

Thermodynamic Analysis of the Relative Effectiveness of Narcotics. FRANK BRINK, PH.D. (Johnson Foundation, Univ. of Penna.). Narcosis is a cellular process apparently reaching equilibrium. For a system of molecules in equilibrium the partial molal-free energy, or chemical potential, of a given type of molecule is the same in all phases of the system. Therefore, in accordance with the definition of thermodynamic activity (Lewis and Randall), this quantity is also constant for each molecule in each phase at equilibrium. These thermodynamic quantities for a narcotic in any part of a narcotized cell are therefore known if they can be determined in the external solution.

The relative effectiveness of numerous narcotics on many different preparations

were compared by calculating the activities corresponding to the measured concentrations in the external solution or gas. If the narcotic concentrations in the aqueous phase were given, the activities were calculated by means of the measured activity coefficients published by Butler (*Trans. Faraday Soc.*, September, 1936). If the data were in the form of partial pressure in a gas phase in equilibrium with the narcotized preparation then the activity was calculated as the ratio of this quantity to the vapor pressure of the pure narcotic at the same temperature. By these procedures the pure narcotic is employed as the standard state of each substance.

The results show that for many narcotics of different chemical structure acting upon a variety of cell types, equal degrees of effect are produced at equal thermodynamic activities. This conclusion contrasts sharply with findings of Ferguson (*Proc. Roy. Soc., B*, 127, 387, 1939) and of Badger (*Nature*, 158, 585, 1946) both of whom emphasize the progressive increase, in an homologous series of compounds, of the thermodynamic activity at which narcosis occurs.

The available data indicate that for the same narcotics either of these orderly relations can occur, depending upon the type of cell studied and the kind of cell function that is being measured.

The rule that for many narcotic substances equal degrees of narcosis are produced at equal thermodynamic activities, though severely restricted by such exceptions, is common enough to be regarded as the simplest law of narcosis. It is suggested that this rule is an important guide for the development of an adequate theory of the molecular mechanism of narcosis.

Action of Narcotics on Synapses Compared to Axons in Sympathetic Ganglia. J. M. POSTERNAK, M.D.,* and M. G. LARABEE, PH.D. (Johnson Foundation, Univ. of Penna.). The action of narcotics on

* Fellow of the Swiss Foundation for medico-biologic studies.

synaptic functions were compared with effects on axonal conduction by recording impulses transmitted through perfused stellate ganglia of cats. The postsynaptic action potential in the inferior cardiac nerve following preganglionic nerve stimulation measured the number of cells responding to synaptic excitation; the action potential of the cervical sympathetic trunk measured the number of Type B fibers conducting impulses through the stellate ganglion without synapse. The effectiveness of a narcotic was measured by the concentrations required to depress the action potentials in these nerves to 50% of their control amplitude.

Chloretone and sodium pentobarbital exhibited preferential action on the synaptic pathway, which was depressed by concentrations respectively about one-seventh and one-eleventh those which equally depressed conduction over B fibers. Chloroform and ethyl ether also depressed preferentially the synaptic pathway at concentrations about one-third those depressing conduction over B fibers to the same extent. Both these narcotics caused detectable depression at concentrations equalling those in blood for human surgical anesthesia.

By contrast, ethyl urethane and ethyl alcohol had no preferential action on synapses. Actually axonal conduction was depressed by concentrations lower than those equally depressing the postsynaptic response.

The preferential action on the synaptic pathway developed progressively in the homologous series of aliphatic alcohols, the ratio of required concentrations being a linear logarithmic function of the number of carbon atoms. For methyl alcohol, a 50% reduction of the action potential of the B fibers was reached with about one-half the concentration required for the same reduction of the postsynaptic response; for octyl alcohol, a 5 times higher concentration was required for B fibers than for the synaptic pathway.

For all these narcotics, a correlation is

shown between their effectiveness and their differential action: the lower the required narcotic concentration, the higher is the preferential action for the synaptic pathway.

For a given effect on the synaptic pathway, thermodynamic activities were nearly equal for ethyl ether, chloroform and the several alcohols, while molar concentrations varied nearly 19,000-fold. For effect on B fibers, the thermodynamic activities for the alcohols increased 10-fold with number of C atoms, from C_1 to C_8 .

Analysis of Skin, Muscle and Brachial Arterial Blood Temperatures in the Resting Normal Human Forearm. H. H. PENNES, M.D. (Psychiatric Inst. of New York). Forearm skin and muscle, brachial arterial blood and rectal temperatures were measured by radiometric and thermocouple techniques in 64 subjects, 30 to 60 years in age (patients of the Neurological Institute, New York, without evidence of neuromuscular disease of the arms). Subjects were basal, nude except for a small sheet over the hips and lay on an ordinary hospital bed with the right forearm supported in air. Air and wall temperatures were identical and ranged from 25 to 27.5° C.;* air relative humidities from 45 to 75%; linear air velocity was always below 20 feet per second.

(a) Mean brachial arterial blood temperature was 36.68° C., mean maximum forearm temperature 36.52° C. in 10 subjects. In each of these subjects the brachial arterial blood temperature was higher than maximum forearm temperature by amounts ranging from 0 to 0.36°.

(b) The longitudinal skin temperature gradients along the superior surface of the long axis of the forearm averaged 0.03° C. per cm. in 14 subjects, a negligible value in the mathematical analysis.

(c) Thermal distributions in 17 subjects around the circumference of the forearm at the experimental plane (8 cm. distal to olecranon process of ulna) were spatio-

* All temperatures are in ° C.

ally non-uniform; average maximum difference between any 2 forearm points was 1.2° C. for the group. In 14 subjects, occlusion of blood flow both through and below the experimental plans showed that these non-isothermal distributions were influenced by the venous return from the distal part of the forearm.

(d) Deep tissue temperature distributions in 9 subjects through the entire transverse axis of the forearm at the experimental plane were approximately parabolic; lack of perfect circular symmetry of the individual curves precluded logarithmic analysis. The mean experimental deep tissue temperature curve was therefore approximated by curves giving the theoretical distributions of tempera-

ture in solid tissue cylinders with uniform rates of heat production and volume flow of blood. The mathematical analysis combined the general differential equation of heat flow in homogeneous, isotropic conductors, the Fick principle of physiology and the Newton Cooling Law. Closest approximation of the experimental data was obtained with substituted values of local tissue heat production of 0.0001 gm. cal. per cm.^3 per second and blood flow of 0.0002 to 0.0005 gm. per cm.^3 per second. If the volume flow of blood and the other necessary data are obtained; then the rate of local resting forearm tissue heat production may be obtained by this analytic method.

BOOK REVIEWS AND NOTICES

APHASIA: A GUIDE TO RETRAINING. By CAPT. LOUIS GRANICH, U. S. Army Med. Admin. Corps. Appendix in collaboration with SGT. GEORGE W. PRANGLE, U. S. Army Med. Corps. Pp. 108. New York: Grune & Stratton, 1947. Price, \$2.75.

It is recognized that aphasic manifestations do not exist alone, since brain injuries often cause "personality changes, some degree of general mental deterioration, and physical handicaps, as well as specific mental disabilities outside of the language functions." Indeed, these may be more obvious than is the aphasia. The following important topics, with their subdivisions, are considered: The Typical Speech Disabilities, Receptive Aphasia, Alexia and Related Disorders Affecting Reading, Agraphia and Related Disorders Affecting Writing.

The retraining of 8 selected cases is given, though no definite outline is followed, and only the significant features are discussed. Case 1 showed an injury to the left parieto-frontal region; part of the technique employed was through copying drills, left hand writing which was rapidly developed, training in articulate sounds, passive moulding of mouth parts, and mirror imitation of mouth movements. In about a month the subject was able to pronounce any sound, he wrote fairly well but scrambled long words, and rhythm was used, beating out time for each syllable. After prolonged patient training, much progress was made, though at the last recording of the case, difficulty was still experienced in sentence formulation. This volume is a valuable contribution to the complex problem of retraining aphasics.

N. Y.

REHABILITATION THROUGH BETTER NUTRITION. By TOM D. SPIES, M.D., Univ. of Cincinnati Studies in Nutrition at the Hillman Hosp., Birmingham, Alabama. Pp. 94; 50 figs. Phila. and London: Saunders, 1947. Price, \$4.00.

THIS volume is a recapitulation of the author's extensive experience with deficiency disease. In it he reiterates the criteria upon

which diagnosis of deficiency of the separate vitamin fractions is made and describes the therapeutic regimen he has employed in relief of such deficiencies. Most of this information is now generally available to the practicing physician due to the pioneering work in the nutrition field to which Dr. Spies himself largely contributed. The present volume adds nothing new, either in information or point of view, but does offer a convenient summarization of Dr. Spies' experience.

K. E.

STANDARD METHODS OF THE DIVISION OF LABORATORIES AND RESEARCH OF THE NEW YORK STATE DEPARTMENT OF HEALTH. By AUGUSTUS B. WADSWORTH, M.D. Foreword by GILBERT DALLDORF, M.D. 3d ed. Pp. 990; 105 figs. Balt.: Williams & Wilkins, 1947. Price, \$10.00.

THIS edition contains over 300 pages more than did the 2d edition. While the sections and chapters are very much the same, in most cases they have been expanded to include recent material. The section on mycology has been enlarged considerably and a new section "Examination of samples concerned with restaurant sanitation" has been added. No mention is made of the use of thioglycollate medium for the sterility testing of biological products containing organic mercurials for preservatives as is required by the U. S. Food and Drug Administration. The book still remains a valuable one for public health laboratories.

H. M.

A MANUAL OF FRACTURES AND DISLOCATIONS. By BARBARA BARTLETT STIMSON, A.B., M.D., Med. Sc.D., F.A.C.S., Ass't Prof. of Clinical Orthopedic Surgery, College of Physicians and Surgeons, Columbia Univ. New York: 2d ed. Pp. 223; 98 ill. Phila.: Lea & Febiger, 1947. Price, \$3.25.

THIS short text is in its 2d edition and represents in a remarkably small space a concise, clearly written handbook on the treatment of fractures and dislocations. Dr.

Stimson has had a wide experience with the effects of trauma on the human body, both on the Fracture Service at the Presbyterian Hospital and in the British Army in World War II. The book can be highly recommended to the medical student and general practitioner as the best short organized guidebook on this subject available.

P. C.

CHEMISTRY AND METHODS OF ENZYMES. By JAMES B. SUMNER, Prof. of Biochemistry, Cornell Univ., and G. FRED SOMERS, Plant Physiologist, U. S. Plant, Soil and Nutrition Laboratory, Ithaca, N. Y. 2d ed. Pp. 415; 10 figs. New York: Academic Press, 1944. Price, \$6.50.

PROGRESS in the fields of enzyme chemistry has made necessary a new edition of this valuable book. Approximately 50 pages of additional descriptive material have been added, and some whole sections have been rewritten. The major additions have been in the sections upon general properties of enzymes, phosphatases (esterases), carbohydrases, and the broad group of enzymes concerned with carbohydrate metabolism, namely, phosphorylases, transphosphorylases, phospho-isomerases and phosphomutases. All other sections have been brought up-to-date, and errors that appeared in the 1st edition have been corrected. The authors make no claim that this is a complete source book of enzyme information. In fact, it was not written for this purpose. Detailed directions are given for the preparation and measurement of the activity of many enzymes by procedures that have been checked thoroughly in their laboratories. The book continues to be the best available for everyone requiring a concise reference volume to the whole field of enzymes and their chemistry.

H. V.

THE CHEMICAL COMPOSITION OF FOODS. By R. A. McCANCE, M.D., Ph.D., F.R.C.P., and E. M. WIDDOWSON, B.Sc., Ph.D., Dept. of Medicine, Univ. of Cambridge. 2d ed. Pp. 156. Brooklyn, N. Y.: Chemical Publishing Co., 1947. Price, \$3.75.

This is the second American edition of a widely used English handbook. Besides tabulating the composition of the various common foods, as purchased, data are also given for them after cooking, with detailed

recipes for preparing the various cooked foods that have been analyzed. The two major sets of tables list the percentage and per ounce composition of each listed food. The tables contain information upon the protein, fat, available carbohydrate, calories, Na, K, Ca, Mg, Fe, Cu, P, Cl, and acid base values. In the English system of analysis the available carbohydrate is determined directly, and all values are computed as monosaccharide. Likewise, the authors compute caloric values by using the factors 4.1, 9.3, and 3.75 for protein, fat and carbohydrate. While the system is not the one ordinarily used in this country, this does not detract from the value of the book; a complete index of all foods analyzed facilitates its use.

H. V.

AN APPROACH TO SOCIAL MEDICINE. By JOHN D. KERSHAW, M.D., (Lond), D.P.H. Medical Officer of Health, Accrington. Pp. 329. Balt.: Williams & Wilkins, 1946. Price, \$4.50.

THE first half of this volume is concerned with the development of society and has little to do with medicine of today, either in the treatment of disease or in public health aspects. It does, however, serve as a setting for Part 2—"Health and Sickness in Society," and this latter half of the book should be of interest to every physician.

The author's thesis is that we should not look upon disease as a pathological entity but as something that interferes with the practice of living. Then our objective becomes the rehabilitation of the social function of the individual and not anatomical restoration. The earlier in disease this objective is applied, the more effective it becomes; the longer it continues, the better the restoration. "The ideal restoration scheme will be integrated at one end with the hospital and at the other with industry."

It is further maintained that health is not merely freedom from disease but a state of "optimum functional efficiency." In order that the physician achieve this for his clientele, his understanding of environmental influences must be developed by a larger participation in research upon and investigation of many social problems such as food, housing, work, leisure, sex, genetics and education. There are a great many references to the literature, mainly of England, and suggestions for further reading. S. B.

ATLAS OF CARDIOVASCULAR DISEASES. By IRVING J. TREIGER, M.D. Ass't. Prof. of Medicine, Univ. of Illinois, Chicago; in Charge of Cardiographic Department, Presbyterian Hospital, Chicago, etc. Pp. 180; 244 ills., 11 in color. St. Louis: C. V. Mosby, 1947. Price, \$10.00.

THE author states that a cross section of common types of heart disease with autopsy findings is presented, with a selection of simple uncomplicated cases. Emphasis is placed on correlation of history, physical findings, roentgenogram and electrocardiogram for purposes of diagnosis and treatment. The atlas is divided into 6 sections: (1) the normal heart, (2) rheumatic disease, (3) arteriosclerotic heart disease, (4) hypertension, (5) syphilitic heart disease, and (6) congenital anomalies. Because of the elementary nature of the material presented, the atlas is doubtless intended for those who know little concerning cardiovascular diseases but wish to familiarize themselves with the findings in what may be called typical cases. Like most atlases, its greatest usefulness will be as a supplement to other forms of study. Cardiovascular diseases in their earlier and clinically more important stages do not yield striking pictures for reproduction in an atlas, and pathological material is more difficult to collect. For example, in this atlas there are no illustrations of the vitally important early stages of cardiovascular syphilis, although aneurysm and aortic insufficiency are adequately presented. Perhaps the most serious criticism that can be made is that the electrocardiograms include only one precordial lead.

C. W.

THE DIAGNOSIS AND TREATMENT OF DIARRHEAL DISEASES. By WILLIAM Z. FRADKIN, A.B., M.D., Assistant Attending Gastroenterologist, Physician-in-charge of Colitis Clinic, Associate Bacteriologist, Jewish Hospital of Brooklyn. Foreword by BURRILL B. CROHN, M.D. Pp. 254; 113 ills. New York: Grune & Stratton, 1947. Price, \$6.00.

A BOOK such as this, stressing the importance of diarrhea and presenting the various conditions causing it, has long been needed. The first 70 pages include the anatomy and physiology of the digestive tract and general methods of treatment, diagnosis and prevention. Subsequently the

diarrheal diseases are discussed individually as to their etiology, pathology, diagnosis and treatment. As stated in the preface, no attempt has been made to describe completely those conditions of which diarrhea is only a part. Thus, under the heading of "Diarrhea caused by hyperthyroidism" the other manifestations of that disease are not presented. This limitation, plus an unusual conciseness, has produced a relatively short, but all-inclusive, book. Fortunately, accuracy and completeness have not been sacrificed for brevity. Confusion or omission is evident in only a few instances: as in the therapy of amebic diarrhea where the use of two or more drugs is advocated but not explained, and in the therapy of several of the conditions due to toxic substances such as arsenic, mercury and mushroom poisoning. A bibliography is included at the end of every chapter for those desiring additional or more general information. The value of the book is enhanced by many excellent illustrations. A few more of these depicting, in greater detail, the microscopic appearance of the intestinal parasites would, however, not be amiss. In view of the prevalence and importance of diarrhea, this book should be of definite value to all internists and general practitioners as well as to students.

R. B.

CURARE, ITS HISTORY, NATURE AND CLINICAL USE. By A. R. MCINTYRE, Ph.D. M.D. Prof. of Physiology and Pharmacology, College of Medicine, Univ. of Nebraska. Pp. 240; 25 ills. Chicago: Univ. of Chicago Press, 1947. Price, \$5.00.

CURARE, once a laboratory curiosity, is now used frequently in clinical medicine. In this monograph McIntyre has gathered together practically every reference to the drug which has appeared from the 15th century through part of 1946. Such a complete summary of the literature should be of interest to the medical historian, neurologist, anesthesiologist, physiologist and pharmacologist. The early history of curare is presented in detail, as is a consideration of the botanical problems involved in identification of the various sources of the drug. One chapter is devoted to chemistry. There are also chapters on the action of curare on nerve and muscle, circulation and respiration, viscera and the central nervous system. The clinical use of curare is also

discussed. The author subscribes more or less to the cholinergic concept of neuromuscular transmission and interprets the action of curare in this light. This may not be acceptable to some readers. The possible rôle of histamine liberation in the picture of curare action and toxicity is omitted. A central nervous system action of curare is accepted on the basis of relatively inconclusive evidence. The bibliography is perhaps too complete. For example there are 178 references listed for 15 pages of Chapter 8. Many of these seem to be included for no particular reason. The format of the book is attractive. The paper is of good quality and the print easy to read.

R. D.

milk sanitation since the late Milton J. Rosenau compared the bacterial content of the Washington City sewage with its market milk, and no flattery to the milk. The second half of the volume concerns food and its importance in the field of environmental sanitation. All details essential to the health officer in his control work are brought to the reader as vividly as though by television. Throughout the need for dependence upon educational methods is emphasized. In the appendix, information is given upon many matters such as: supplementary source material, field equipment for inspectors, courses of instruction, the application of DDT, list of films relating to milk and the precision testing of high-temperature short-time pasteurizers.

A. H.

MILK AND FOOD SANITATION. By H. S. ADAMS, B.Sc. Division of Public Health, Minneapolis. Pp. 311; 65 ills. New York: The Commonwealth Fund, 1947. Price, \$3.25.

WHEN the need for advice upon sanitation is recognized by a lay person the family doctor should be a reliable consultant. Whether he is or not, depends on many factors. An important one among these may well be the lack of a modern, attractive and factual text: one in which the clearly cut answers are so arranged and indexed that they can be easily and quickly identified. For practical information upon the best current practice in the sanitary production, handling and distribution of milk and other foods, this volume will satisfy every inquirer: the family doctor, the professional sanitarian, the person who wants to know. To have recognized the great general need for this book is an achievement in itself; to have satisfied a high ambition in its production is to aid all our communities toward better living. The first half of the book concerns milk, its history, its nutritive value, the public health problems connected with it and its economic importance. Then the author seems to take the health officer by the hand and lead him gently, but firmly and expertly, through all the details of building a high quality milk program and maintaining it. All the essentials of sanitary milk production, pasteurization and distribution are described in careful detail, with generous recognition and citation of the work of others. Nothing better has been written on

MEDICAL CLINICS OF NORTH AMERICA. Mayo Clinic Number. Blood Transfusions and Rh Factor. Pp. 785-1058. Phila.: W.B.Saunders, 1947. Price, \$16.00 a year.

THE title of this issue is misleading, as only 5 articles deal with the subject. The remaining 15 articles cover a wide variety of subjects of interest to the general practitioner. The paper on radiophosphorus is well written and covers the limitations of this substance quite adequately. Of special interest is the article on duodenal ulcer by Thomas B. Magath, which again emphasizes the important conditions to be considered in the differential diagnosis of perforated duodenal ulcer. An article on atomic energy in medical practice generalizes on the medical values of atomic research and on some of the beneficial results that may be obtainable from substances with such destructive potentialities.

J. F.

FORENSIC MEDICINE. By KEITH SIMPSON, M.D., Lecturer in Forensic Medicine, Guy's Hospital, Examiner in Forensic Medicine, Univ. of London. Pp. 335; 114 ills. Balt., and London: Williams & Wilkins, 1947. Price, \$4.50.

THIS book, though pocket size, is a comprehensive presentation of Forensic Medicine. It covers the entire field with emphasis on the pathological side, *i. e.*, autopsy procedure, wounds, signs of death, cause of death, blood stains, identity. The section on Toxicology is also well done, and includes

such new drugs as D.D.T. and the poison gases. Criminal Abortion and Infanticide are given full and adequate consideration.

In the field of Civil Malpraxis, Negligence, and Psychiatry, while these subjects are well presented from the British standpoint, the difference between English and American practice not only becomes evident but is a serious drawback to the use of the book in this country. The classification of the insanities has been simplified and differs from that commonly used here. Such an important subject for forensic practice as the Psychopathic Personalities is not even considered. The age of consent, epilepsy as a defense for murder, the juvenile aspects of crime, and many other subjects, too, are presented purely from the English standpoint, as is Workmen's Compensation. While it may appear captious to point out these differences, if this textbook obtains the circulation among American doctors and students that it deserves, an edition incorporating American law and practice, would be well worthwhile. The book is fully illustrated, in color and in black-and-white, and has an excellent index. It "is designed to provide a brief and essentially practical guide to current teaching of Forensic Medicine." As such, it is the best in its field.

D. McC.

because finer cytologic changes are hazy. In short, some of the illustrations are not diagnostic even when the lesion is of the kind that is diagnostic, and most of them do not adequately portray the order of pathologic process, even, in the case.

Typographic errors are few: in some places the names of diseases are capitalized; Senear's name reads "Sennear." The more serious omissions of diseases consist in the blastomycoses, coccidioidal granuloma, senile keratosis, parafinoma and bromide granuloma.

Errors in the actual content are few—one surmises that the seborrheic keratosis figured on page 311 is the hard nevus of Unna, and that the nevus pigmentosus on page 315 is a seborrheic keratosis. The illustrations on page 321 might equally be a blue nevus, such as is so inadequately portrayed on page 331, although the reviewer is aware of the different viewpoints as to pathologic concepts and terminology of the pigmented nevi.

The authors deserve credit for their enterprise and energy. They have succeeded in portraying the larger patterning aimed at, but when cytologic detail becomes involved there is much to be desired. In short, the book will be found useful only up to a certain point, both for the trained pathologist and the graduate student in dermatology.

F. W.

ATLAS OF HISTOPATHOLOGY OF THE SKIN.

By G. H. PERCIVAL, M.D., A. MURRAY DRENNAN, M.D., and T. C. DODDS. Pp. 495; 376 color photomicrographs. Balt.: Williams & Wilkins, 1947. Price, \$16.00.

THIS is a collaborative work by a dermatologist, a pathologist and the supervisor of the Laboratory of Pathology at the University of Edinburgh. Being an atlas, there is only a brief sketch of explanatory text preceding each section and so interpretations of pathologic processes have been sacrificed.

As to the illustrations, the first impressions are pleasing because they remind one of the familiar scenes under the microscope. More critical study, though, leads to the realization that many of them are inadequate either for the novice or the trained pathologist. It is true that the general patterning of the lesions is usually satisfactory; both in this respect and in sharpness of detail, the low power magnifications are fairly satisfactory, but high power ones are frequently worthless

NEW BOOKS

American Pharmacy. Vol. II. Edited by RUFUS A. LYMAN, M.D., Director, School of Pharmacy, Univ. of Arizona. Pp. 379; ills. Phila.: J. B. Lippincott, 1947. Price, \$7.00.

Hormones and Behavior. By FRANK A. BEACH, Prof. of Psychology, Yale Univ. Pp. 368. New York: Hoeber, 1948. Price, \$6.50.

Surgical Treatment of the Abdomen. Edited by FREDERIC W. BANCROFT, M.D., F.A.C.S., Prof. of Clinical Surgery, New York Medical College, and PRESTON A. WADE, M.D., F.A.C.S. Pp. 1026; 457 ills., and 3 color plates. Phila.: J. B. Lippincott, 1947. Price, \$18.00.

Teaching Psychotherapeutic Medicine. Edited by HELEN LELAND WITMER, Ph.D. Pp. 464. New York: The Commonwealth Fund, 1947. Price, \$3.75.

Medicine. Vol. I. The Patient and His Disease. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Physician to the London Hospital and Dean of the Medical School. Pp. 383. Balt.: Williams & Wilkins, 1947. Price, \$6.00.

Pharmacology and Experimental Therapeutics. By HAMILTON H. ANDERSON, FUMIKO MURAYAMA and BENEDICT E. ABREU. Pp. 368. Berkeley and Los Angeles: University of California Press, 1947. Price, \$6.50.

Kurze Klinik der Ohren-, Nasen- und Halskrankheiten. By DR. ERHARD LÜSCHER. Pp. 513; 201 ills. Basel: Benno Schwabe & Co., 1948. Gebunden Fr. 54.

American Medical Research Past and Present. By RICHARD H. SHRYOCK, Ph.D., Prof. of History and Lecturer in Medical History, Univ. of Pennsylvania. Pp. 350. New York: The Commonwealth Fund, 1947. Price, \$2.50.

Pathologisch - anatomische Untersuchungen über leberzirrhose bei Säuglingen und Kleinkindern (infantile Leberzirrhose) mit endemischer Häufung. By DR. MED. HERMANN GÖGL. Pp. 155; 29 ills. Wien: Wilhelm Maudrich, 1947. (Imported by Grune & Stratton.) Price, \$7.75.

Congenital Malformations of the Heart. By HELEN B. TAUSSIG, M.D., Assoc. Prof. of Pediatrics, Johns Hopkins Univ. School of Medicine. Pp. 618; 223 ills., 46 in color. New York: The Commonwealth Fund, 1947. Price, \$10.00.

Mental Health. By JOHN H. EWEN, F.R.-C.P.E., D.P.M., Physician and Lecturer in Psychological Medicine, Westminster Hosp.; Med. Superintendent, Springfield Mental Hosp., London. Pp. 270. Balt.: Williams & Wilkins, 1947. Price, \$4.00.

MENTAL health problems have become a matter of national concern, and this book offers fundamental knowledge to the student, the general practitioner, those dealing with social and educational problems, child welfare, delinquency and special matters of industry. Preference is shown for the term, psychological medicine, since subjects may range from mild eccentricities to major psychoses. The sections on psychoneuroses and psychoses are concise and lucid. Almost 25 pages are given to the various English legal aspects, which laws the writers hope may be improved. Obviously, the section does not meet our needs; otherwise, the book is admirable.

N. Y.

Dermatology for Nurses. By G. H. PERCIVAL, M.D., Ph.D., Grant Prof. of Dermatology, Univ. of Edinburgh, and ELIZABETH TODDIE, S.R.N. Pp. 116; 73 ills. Balt.: Williams & Wilkins, 1947. Price, \$4.50.

"THE aim of this book is to present a detailed account of the nursing of the common diseases of the skin for nurses who have received no systematic teaching in the subject." (Preface.)

Radium Dosage. The Manchester System. Edited by W. J. MEREDITH, M.Sc., F.-Inst.P., Christie Hospital and Holt Radium Institute, Manchester. Pp. 124; 4 plates. Balt. and London: Williams & Wilkins, 1947. Price, \$4.50.

"THE purely physical aspects of the work can be found in Part II which consists of the physical sections of the papers presented almost completely in their original form." (Preface.)

Psychopathology and Education of the Brain-injured Child. By ALFRED A. STRAUSS and LAURA E. LEHTINEN. Pp. 206; 46 ills. New York: Grune & Stratton, 1947. Price, \$5.00.

"THIS book deals with those children, physically handicapped or physically sound, who show intellectual and personality aberrations as a result of injury to the brain substance." (Introduction.)

Manual de Micologia Clinica. By NORMAN F. CONANT, Ph.D., DONALD STOVER MARTIN, M.D., DAVID TILLERSON SMITH, M.D., ROGER D. BAKER, M.D., and JASPER LAMAR CALLAWAY, M.D., Traducción y adaptación por el Prof. Dr. GUSTAVO PITALUGA. Pp. 456; 148 ills. Havana, Cuba: M. V. Fresneda, 1947. Price not given.

ANOTHER volume of the series published under the auspices of the Division of Medical Sciences of the National Research Council to disseminate information of value in military medicine.

NEW EDITIONS

Gynecological and Obstetrical Urology. By HOUSTON S. EVERETT, M.D., Assoc. Prof. of Gynecology, the Johns Hopkins Univ. 2nd Ed. Pp. 539; 232 ills. Balt.: Williams & Wilkins, 1947. Price, \$6.00.

Public Health Administration in the United States. By WILSON G. SMILLIE, M.D., Dr.P.H., Prof. of Public Health and Preventive Medicine, Cornell Univ. Medical College. 3rd Ed. Pp. 637. New York: Macmillan, 1947. Price, \$6.50.

Biochemistry for Medical Students. By WILLIAM VEALE THORPE, M.A. (CAN-TAB.), PH.D. (LOND.), Reader in Chemical Physiology, Univ. of Birmingham. 4th Ed. Pp. 496; 36 ills. Balt. and London: Williams & Wilkins, 1947. Price, \$5.00.

"A new chapter on the Use of Isotopes in Biochemical Investigations, which could not be included in the previous edition owing to paper restrictions, has now been added. Much other new material has been incorporated and the sections on protein structure, co-enzymes, flavoproteins, bile pigments and nutrition in wartime have been largely rewritten." (Preface.)

Recent Advances in Sex and Reproductive Physiology. By J. M. ROBSON, M.D., D.Sc., F.R.S.E., Reader in Pharmacology, Guy's Hospital Medical School, Univ. of London. 3rd Ed. Pp. 336. Phila.: Blakiston, 1948. Price, \$5.75.

Blood Pressure and Its Disorders, Including Angina Pectoris. By JOHN PLESCH, M.D., formerly Prof. of Internal Medicine, Univ. of Berlin. 2nd Ed. Pp. 307; 125 figs. Balt.: Williams & Wilkins, 1947. Price, \$6.00.

A Text-Book of Bacteriology. By R. W. FAIRBROTHER, M.D., D.Sc. (MAN.), F.R.C.P. (LOND.), Special Lecturer in Bacteriology, Univ. of Manchester. 5th Ed. Pp. 480; 6 ills. New York: Grune & Stratton, 1948. Price, \$6.00.

Treatment of Some Chronic and "Incurable" Diseases. By A. T. TODD, O.B.E., M.B. (EDIN.), M.R.C.P. (LOND.). 2nd Ed. Pp. 324. Balt.: Williams & Wilkins, 1947. Price, \$7.00.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P., Prof. of Pathology, Univ. of London, and LAWRENCE P. GARROD, M.D., F.R.C.P., Prof. of Bacteriology. 5th Ed. Pp. 362; 60 ills. Phila.: Blakiston, 1948. Price, \$6.00.

THIS volume differs from previous editions by the addition of a new chapter on the liver, and the inclusion of recent experimental work on cancer and on inflammation. The authors attempt to summarize important developments of the last 2 decades in selected major fields. By and large, the volume contains little that does not appear in recent editions of the standard textbooks. A. R.

A Text-book of Mental Deficiency (Amentia). By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S. (EDIN.), Consulting Physician to Univ. College Hospital, London. 7th Ed. Pp. 534; 47 ills. Balt.: Williams & Wilkins, 1947. Price, \$8.50.

THIS is a book of recognized value, and the current edition, which includes much new material, is planned to meet the needs of the psychiatrist and psychologist, the general practitioner, and the medical officers of public authorities and institutions. The English laws, included, are not wholly applicable here. N. Y.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

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ORIGINAL ARTICLES

HISTOPLASMOSIS AND TORULOSIS AS CAUSES OF ADRENAL INSUFFICIENCY

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SINCE the time of Thomas Addison it has been recognized that tuberculosis is the most frequent cause of the syndrome of adrenal insufficiency due to massive destruction of the glands. It is well known, however, that other microorganisms as well as neoplasms may destroy enough adrenal tissue to produce the signs and symptoms of adrenal insufficiency. It is our purpose in the present communication to point out the less well known fact that certain fungus diseases, by means of massive destruction of the adrenal glands, may

likewise produce the syndrome of insufficiency of adrenal hormones. It is felt that despite their relative infrequency, histoplasmosis and torulosis should be kept in mind in any differential diagnosis of the syndrome. We have therefore reviewed all cases of adrenal involvement by histoplasmosis and by torulosis available to us, and present an analysis of the data in Tables 1 and 2.

In Table 1, it will be noted that a total of 19 cases (including Case 1 herein reported) of involvement of the adrenal

TABLE 1.—SUMMARY OF REPORTED LESIONS OF THE ADRENAL GLANDS CAUSED BY HISTOPLASMA CAPSULATUM AND BY CRYPTOCOCCUS NEOFORMANS (TORULA HISTOLYTICA) (INCLUDING PRESENT CASES)

Type of lesion	Number of cases	
	Histoplasmosis	Torulosis
Presence of organisms with or without foci of inflammatory cells	41,10,17,20	54,6,24
Partial necrosis without symptoms of adrenal insufficiency	42,9,12,21	118
Massive necrosis with adrenal insufficiency (including present cases)	915,16,17,22,23,25	1
Not stated	23,7	113
Totals	19	8
Per cent of described lesions showing caseation	76%	28%

glands by *Histoplasma capsulatum* have been reported. Of these, 12 have shown some degree of destruction of adrenal parenchyma, and in 9 there was massive

destruction of such magnitude that death was presumably due to adrenal insufficiency. In Table 2 it will be noted that some symptoms of adrenal insufficiency

TABLE 2.—ANALYSIS OF CASES OF ADRENAL INSUFFICIENCY CAUSED BY HISTOPLASMA CAPSULATUM

Case reported by	Age	Sex	Race	Symptoms suggestive of adrenal insufficiency	Adrenal weight (gm.)	Description of adrenals
1. Parsons and Zarafonetis ¹⁷ (Case 24), 1938*	63	M	W	Weight loss, dehydration	50 60	Almost complete caseation necrosis surrounded by granulation tissue. Yeast present.
2. Parsons and Zarafonetis ¹⁷ (Case 53), 1940	49	M	W	Anorexia, severe weakness, B.P. 88/62, wt. loss	70 65	Firm gray tissue mixed with yellow areas of necrosis. No adrenal tissue seen.
3. Manchester, 1941 (quoted by Parsons and Zarafonetis ¹⁷)	63	M	W	"Evidence of adrenal insufficiency"	Not stated	Bilateral adrenal necrosis. Organisms in adrenals only.
4. Palmer, Amolsch and Shaffer, ¹⁸ 1942	45	M	W	Weakness, emaciation, B.P. 95/55	Not stated. Size 7 x 3.5 x 1 cm.	Rubbery, caseous many tubercles and pseudo-tubercles.
5. Van Pernis, Benson and Holinger, ²³ 1943	63	M	W	Marked weakness, 80 lb. wt. loss, bronzing of skin	14.2 14.5	Thick fibrous capsules surround yellow-gray caseous tissue containing many yeasts.
6. Thomas and Morehead, ²² 1943*	44	M	W	Marked weakness, severe respiratory infection, B.P. 80/64. Weak pulse	36 52	Almost entirely replaced by light gray fibro-caseous material
7. Martin and Silber, ¹⁹ 1944	39	F	W	Marked weakness, wt. loss of over 45 lbs., gradual fall in B.P. from 194/110 to 100/60	Not stated. Rt. twice normal size. Left 10 x 5 x 4 cm.	Entire left gland replaced by firm nodular white tissue with caseous center. Right gland contained numerous nodules.
8. Ziegler, ²⁵ 1946	58	F	W	Severe weakness, 70 lb. wt. loss, anorexia	Not stated. Size: 9 x 5 x 3 cm., and 7 x 4 x 2 cm.	Grayish yellow tissue with hemorrhage and necrosis. Only slight cortical remnants.
9. Rawson, Collins and Grant (Case 1), 1947	62	F	W	Marked weakness, wt. loss, fall in B.P.	60 65	Both glands replaced by caseous material surrounded by fibrous tissue.

* Co-existing pulmonary tuberculosis.

such as marked weakness, anorexia, dehydration, weight loss, low blood pressure, and bronzing of the skin were present in each case where massive adrenal destruction was found at autopsy. For the most part the importance of these symptoms was masked by other complaints referable to the involvement of other organs. It will further be noted that the appearance of the adrenal gland at autopsy was rather uniform. There was marked enlargement, and almost complete parenchymal replacement by yellowish-gray fibrocaseous tissue containing the causative organism.

Involvement of the adrenals by *Cryptococcus neoformans* (*Torula histolytica*) has been noted far less frequently. In Table 1 it is seen that only 8 such cases have been reported. Only 2 of these showed any necrosis, and in only 1 (Case 2 herein reported) was there necrosis extensive enough to produce the syndrome of adrenal insufficiency. Case reports of adrenal insufficiency caused by histoplasmosis and by torulosis, respectively, follow:

Case Reports. CASE 1. Mrs. A. K., a 62 year old white female, had always enjoyed

excellent health until 2 months earlier when, for no apparent reason, she developed a small ulcer on the left ventral anterolateral aspect of her tongue. The lesion was quite painful from the start. Smears for Vincent's and acid fast organisms were negative. In spite of local therapy, the pain persisted and the ulcer slowly increased in size. A biopsy of the tongue lesion was diagnosed as "granuloma." Following the biopsy the wound remained quite indolent and very painful.

The remainder of her previous medical history was not contributory. She had lived in or about Philadelphia all of her life. There was no history of contact with animals.

Temperature was 98° F., pulse rate 80, respirations 20, blood pressure 130/80, weight 137 pounds. Over the tip of her nose there were a few dilated venules. Her skin color was normal. On the left anterolateral aspect of her tongue there was a rather deep granulating wound, measuring 2 x 1.5 cm., covered by a light gray exudate. There was no significant lymphadenopathy. A moderate general diffuse cystic enlargement of the thyroid was present. Over the skin of the upper chest both anteriorly and posteriorly there were many small papillomas, light chocolate in color. No other areas of pigmentation in the skin or oral mucous mem-

brane could be seen. The remainder of the physical examination revealed no further abnormalities. Urinalysis revealed a normal urine. Hemoglobin was 85%; RBC 4,370,000; WBC 5300 (Diff.: Polymorphonuclears 62%; lymphocytes 37%; eosinophiles 1%). The Kahn test was negative. A Roentgen ray of the chest, and a basal metabolic rate were both normal.

Therapy consisted of a high vitamin diet, and saturated solution of potassium iodide 5 drops 3 times a day. Within a few days she stated that she felt much better and that the pain in her lingual ulcer had almost completely disappeared. As the granulating wound on her tongue was now healing rapidly therapy was discontinued. Two months later, however, a gingival ulcer appeared in the lower incisor area on the buccal aspect. Within a few days this ulcer rapidly increased in size until its diameter was 1.5 cm. The edges were sharp, and the center was deeply excavated exposing about 50% of the cervical portion of the 2 lower central incisor teeth. Potassium iodide was immediately re-ordered—at first 5 drops, then 10 drops 3 times a day. The favorable effect that had been noted with its first administration was not now seen however.

On October 26, 1946 it was noted that her weight was 129 pounds. She had some dyspnea on slight exertion, and it was evident that her condition was becoming worse. There was vague abdominal discomfort. The gingival ulcer was showing no tendency to heal and it was very painful. On January 24, 1947 she was admitted to this hospital because of the onset of fever, and her poor general condition. Weight on admission was 123 pounds. Blood pressure was 120/80. Temperature was 100° F. The liver was now palpable 10 cm. below the right costal margin. It was not tender and the edge was smooth. The remainder of the physical examination revealed no significant change.

Chest Roentgen ray and gastro-intestinal Roentgen ray study were normal. Smears from the gingival ulcer showed some Vincent's organisms but no acid fast organisms were demonstrated. The blood count and sternal marrow smear were normal. The sedimentation rate was 55 mm. per hour. Serum protein was 5.5 gm. %; with 3.3 gm. of albumin and 2.2 gm. of globulin. Urine examinations were consistently negative, and no Bence-Jones protein was found.

On February 12, 1947 her weight was 117 pounds. An irregular fever, varying between 100° and 102° F. was present. Anorexia and weakness were striking. A gingival ulcer which had appeared on the buccal aspect in the region of the 2nd right upper molar and the ulcer in the incisor area remained extremely painful and were uninfluenced by treatment.

During the latter part of February the asthenia increased, and an additional ulcer appeared on the hard palate. It was noted that the blood pressure was falling, now being 90/70. Skin tests to blastomycin, sporotrichin, coccidioidin, and histoplasmin were reported as negative. The patient lost ground very rapidly. Sodium chloride, orally and intravenously, and adrenal cortical extract were ineffective in raising the blood pressure. Death occurred March 2, 1947. It was thought that the symptomatology and clinical course were compatible with the diagnosis of: (1) Histoplasmosis; (2) acute adrenal failure. Culture of the oral lesions (reported several days) gave *Histoplasma capsulatum*.

Autopsy (5 hours after death). The body weighed 48 kg. The principle gross findings were: (1) bilateral enlargement and massive caseation necrosis of the adrenal glands; (2) miliary tubercle-like structures disseminated throughout the lungs, liver, spleen, kidneys, and lymph nodes, and (3) gingival ulcers. Ulcerated lesions were present on the hard palate, and on the gum adjacent to the lower incisor teeth. The tongue appeared normal. There was a diffuse colloid goiter. The heart weighed 170 gm. and had the appearance characteristic of brown atrophy. The lungs were bulky and emphysematous. The cut surface was diffusely studded with minute translucent, grayish miliary nodules. The liver weighed 1430 gm. The cut surface was a homogeneous light tan without distinct lobular markings, and with poorly defined miliary nodules, similar to those in the lung, scattered throughout. The spleen weighed 230 gm. Miliary nodules were scattered throughout. The follicles were prominent; the pulp was brick-red. The adrenals weighed 60 gm. (left), 65 gm. (right). Both were greatly enlarged and were replaced by firm grayish-white fibrocaseous material with hemorrhagic areas. No tissue suggestive of adrenal parenchyma was noted (Fig. 1). In



FIG. 1.—Gross appearance of an adrenal gland (Case 1). The gland has been sectioned and laid open. Note the caseous material and fibrous tissue which appear to have entirely replaced the adrenal parenchyma.

the *kidneys*, miliary nodules were scattered throughout the cortex, and whitish streaks following the direction of the tubules were present in the medulla. Otherwise their structure appeared normal. Caseous areas were present in the aortic *lymph nodes*. The remaining organs appeared grossly normal.

Microscopic Examination. *Adrenals.* Very little adrenal tissue was present; most of the

tissue was caseous. At the periphery of the caseous tissue there was granulation tissue consisting of proliferating fibroblasts among which round cells and giant cells were scattered. At the junction of the caseous and granulation tissues were large mononuclear cells containing innumerable histoplasma; many of these organisms were acid fast (Fig. 2). *Gingival Ulcer:* The mucosa was absent in places. The papillae were heavily

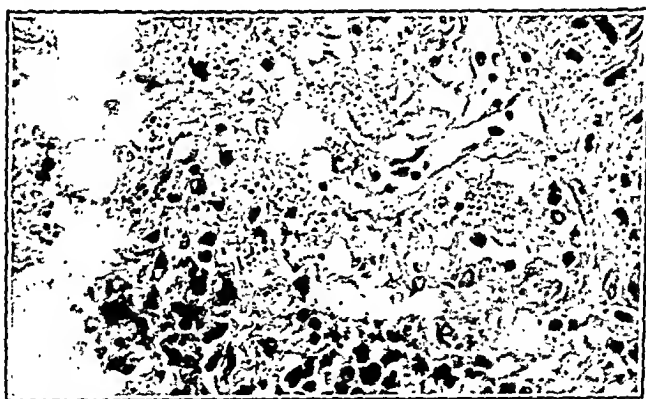


FIG. 2.—Photomicrograph of adrenal (Case 1). Giemsa stain (high power). Note the numerous yeast-like organisms with surrounding clear halo, which are present in large macrophages.

infiltrated with round and plasma cells. In the submucosa there was perivascular round cell infiltration, and numerous organized tubercles containing giant cells of the Langhans type. No organisms of any kind were demonstrated. *Lungs:* Scattered throughout were innumerable round, well-formed nodules consisting of clustered epithelioid cells

arranged in no particular pattern. About the periphery of the nodule was a moderate number of lymphocytes; a few polymorphonuclear leukocytes were scattered throughout the lesion. Some nodules contained central giant cells, frequently of the Langhans type. No organisms of any kind were demonstrated in the lesions. *Spleen:* The pulp was pep-

pered with nodules very similar to those described in the lung. Organisms were not seen. *Liver*: There was atrophy of the parenchymal cell cords. Scattered throughout were miliary nodules less well defined than those in the lung. Epithelioid cells were less prominent. The lesions consisted principally of necrotic hepatic cells and polymorphonuclear leukocytes. A few eosinophils were present in the lesions. Giant cells were very rare, and those seen had the appearance of the foreign-body type of cell. Organisms were not seen. *Heart*: A few granulomatous nodules similar to those seen in the lung were scattered throughout the myocardium. *Kidney*: In the cortex, lesions were found similar to those in the lungs, but less well defined. In the pyramids there were large clusters of epithelioid cells and polymorphonuclear leukocytes which tended to follow the direction of the collecting tubules. *Lymph Nodes*: Were virtually replaced by innumerable miliary granulomata similar to those in the lungs. *Final Diagnosis*: Histoplasmosis, producing massive caseous necrosis of both adrenal glands, disseminated granulomata in heart, lungs, liver, spleen, kidneys, lymph nodes, and ulcerating granulomata of oral mucosa.

CASE 2. Mrs. M. H., a 41 year old white farmer's wife, gave a history of generalized intermittent headaches for 15 years. On April 21, 1947, she had been struck on the head in the right frontal region by a rake handle; the skin was not broken. Subsequently she was nauseated and vomited in the mornings. Vision became blurred in the left eye, and the headaches became worse, radiating over the left side of the head. Because of excessive fatigue and weakness, she was in bed for 5 weeks before being admitted, on June 6, 1947, to the Geisinger Hospital, to which we are indebted for the following information:

On admission, physical examination revealed an obese well-developed white female not appearing ill. Temperature was normal; blood pressure was 135/80 in both arms. Eye examination revealed 20/25 vision in the right eye; vision in the left eye enabled her only to count fingers at 2 feet. There was a ciliary flush in the left eye with debris on the posterior corneal surface and stringy floating vitreous opacities. Enlarged, diseased tonsils were found; the mouth was edentulous. The remainder of the physical

examination, including a neurologic examination, revealed no further abnormalities. Lateral skull and mastoid films were normal. Lumbar puncture on June 9 revealed clear, colorless fluid under an initial pressure of 190 mm., that rose to 410 mm. on jugular pressure, followed by prompt fall. The fluid contained 51 cells per c.mm., mostly lymphocytes, with 150 mg. of protein per 100 ml. Blood sugar was 115 mg. per 100 ml. Repeated urinalyses were normal. A diagnosis of bilateral anterior and posterior uveitis and possible brain abscess or tumor was made.

After a course of 40,000 units of penicillin every 3 hours, she was discharged improved. At home her vision grew worse, and by July 10 she was unable to walk due to weakness of the legs. She was irrational, confused, and mentally sluggish. On July 17 she was brought to this hospital.

Systemic review on admission here revealed a history of a chronic cough that had lasted for many years, productive of $\frac{1}{2}$ cup of white sputum daily. The patient had always been overweight. She had suffered with nocturia and mild leukorrhea, and had had chronic backache for many years. She had undergone appendectomy and right oophorectomy in 1932. Family history was not contributory.

Physical examination revealed an obese, cyanotic white female. Blood pressure was 110/80, pulse 80 and weak, respirations 24, and temperature 98° F. Tonsils were hypertrophied, and the pharynx was injected. Neurologically, she was incoherent, depressed, torpid and stuporous. The left pupil was dilated and fixed, the right was normal. There was questionable weakness of the right arm. Sensory perception appeared normal. The left corneal reflex was missing, otherwise all reflexes were normal. Tentative diagnosis was brain abscess or subdural hematoma.

Ophthalmologic consultation described the left eye as showing marked ciliary flush, slight haziness of the cornea, normal finger tension, many pigmented keratic precipitates and massive vitreous exudation through which no fundus details could be seen except for a large white choroidal lesion in the upper temporal midperiphery. This was similar in appearance to the lesions seen in tuberculous uveitis.

Laboratory findings: hemoglobin 70%; leukocyte count, 14,000 per c.mm.; blood

urea nitrogen, 49 mg. per 100 cc.; fasting blood sugar 62 mg. per 100 cc. Urinalysis: specific gravity 1.008, acid, no albumin or sugar, 2 to 3 RBC and 10 to 15 WBC per high power field, no casts, occasional epithelial cells. Urine culture showed an intermediate strain of *E. coli*. Kolmer and Kline tests negative.

Course in hospital: Patient remained in much the same condition during her first hospital day. Suddenly and without warning, 21 hours after admission, she expired.

AUTOPSY (2 hours after death). The body was that of an obese white female weighing 81 kg., and measuring 160 cm. There was marked generalized cyanosis. *Heart*: weighed 270 gm. and appeared normal except for mild coronary sclerosis. *Lungs*: Right weighed 280 gm., left 230 gm. While these appeared grossly normal, microscopically they showed moderate atelectasis, with

areas of mild compensatory emphysema. No organisms were seen. *Liver*: Weighed 1450 gm. and appeared normal both grossly and microscopically. *Spleen*: Weighed 280 gm. It was a little larger and softer than usual, with purplish-gray surface. On cut section the pulp was brick-red and the trabeculae and follicles distinct. Microscopically, it appeared normal. *Pancreas*: Appeared normal grossly and microscopically. *Adrenals*: The right weighed 22 gm., the left 30 gm. Both were increased in consistency. On cut section there was an escape of thick whitish purulent liquid, which was odorless. The normal adrenal architecture was absent, cortex and medulla of both glands apparently being entirely replaced by the soft white material, surrounded by an ill defined firmer capsule (Fig. 3). Microscopically, the entire gland was seen to be replaced by eosinophilic, necrotic tissue containing many round, clear



FIG. 3.—Gross appearance of an adrenal gland (Case 2). The gland has been sectioned. Note the large areas of caseous material separated by fibrous bands.

spaces, varying in diameter up to 30 micra; in most of these there were round refractile bodies with evidence of internal structure. A few of these took the hematoxylin stain, but most were colorless (Fig. 4). There was much variation both in their size and refractility. In addition to the caseation necrosis there was a fibrous reaction in which actively proliferating fibroblasts appeared to be walling off the caseous tissue. In the fibrous zone there were collections of lymphocytes and giant cells of the foreign-body type (Fig. 5). No recognizable adrenal tissue was found. Ziehl-Nielsen stains of the sections revealed no acid-fast bacilli. The refractile bodies did not take this stain. Gram stains tinted some of the organisms a faint blue. India Ink preparations made from scrapings

of the cut surface showed doubly refractile, round bodies, varying in diameter from 5 to 30 micra, surrounded by a thick clear capsule. Many of the organisms showed budding, with dumb-bell and figure-eight forms. Some contained refractile bodies 3 to 5 micra in diameter, often arranged in clusters placed eccentrically in the cell. These organisms satisfied the morphologic description of *Cryptococcus neoformans* (*Torula histolytica*); their identity was confirmed by Dr. Fred Weidman. *Kidneys*: The right weighed 120 gm., the left 130 gm. They appeared grossly normal. Microscopically, the capsule of the right kidney was somewhat thickened, with small collections of polymorphonuclear leukocytes scattered through the cortex. Adjacent to one such

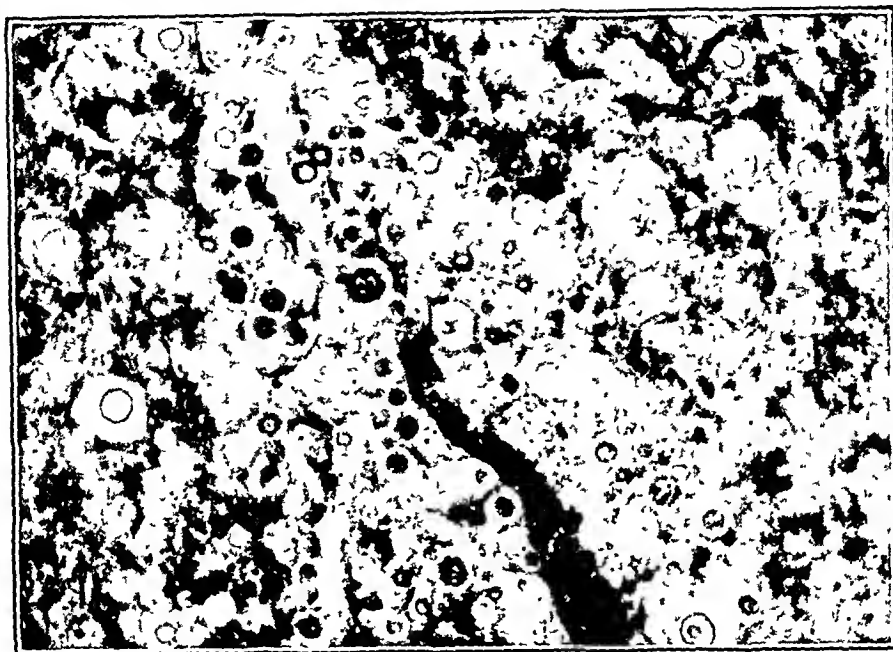


FIG. 4.—Photomicrograph of adrenal (Case 2). Hematoxylin-eosin (high power). Note the round refractile organisms with clear enveloping halo. Some organisms have taken the hematoxylin stain; others have not. The organisms lie free in the tissue

collection, embedded in the necrotic wall of a tubule, was a cluster of *cryptococci*. These were the only organisms found in the kidneys. The left kidney showed less capsular thickening, but similar cell collections. Both kidneys showed numerous collections of

granulocytes lying in and around the collecting tubules. The glomeruli were essentially unchanged. There was an occasional pigment cast. Acid fast stains of the sections revealed no acid fast bacilli. *Brain*: The brain weighed 1250 gm.; the meninges and

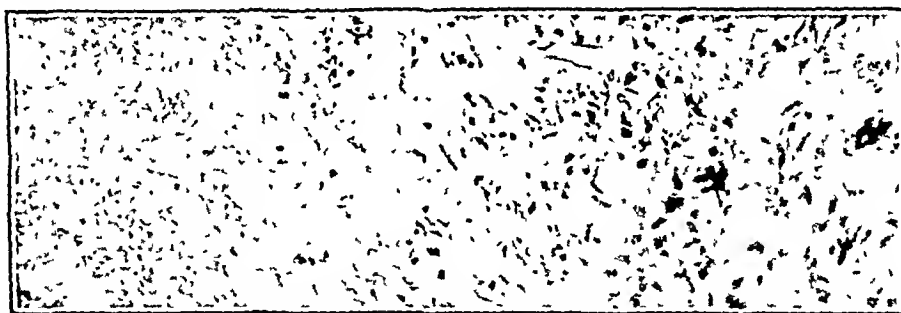


FIG. 5.—Photomicrograph of adrenal (Case 2). Hematoxylin-eosin (high power). Note the fibrous tissue reaction, the giant cells, and the necrotic area.

brain substance appeared grossly normal. Microscopically, some of the sections showed a chronic meningitis consisting of round cell infiltration, rare giant cells, and proliferation of fibroblasts. In the adjacent cortex, were round bodies about the size of torula which took the hematoxylin stain. No capsules or refractile forms could be demonstrated. All other organs appeared grossly and microscopically normal. Permission for the removal of the eyes was not obtained. The final diagnosis was torulosis, causing massive

necrosis of both adrenals, and focal lesions in the kidneys. It is probable that the eye and meningeal lesions were also manifestations of torulosis.

Comment. Among the multiplicity of symptoms caused by a disseminated fungus disease, the diagnostician is apt to overlook possible indications of failure of the adrenal glands. Such symptoms as weakness, anorexia, weight loss and dehydration are not diagnostic in themselves,

and indeed may be merely results of a febrile state. Except in the terminal stages, however, both histoplasmosis and torulosis are characterized by a low-grade fever; the marked weakness and enormous weight loss in those cases that show massive adrenal destruction at autopsy are out of all proportion to the febrile response. While terminal fall in blood pressure is frequent in the cases of adrenal destruction caused by these diseases, the sign appears too late as a rule to be clinically helpful. Bronzing of the skin was noted in but 1 case (Case 5, Table 2).

The 2 cases presented in the present communication both showed definite symptoms of adrenal insufficiency. These were recognized during life in the first case, but not in the second. In Case 1 the disease appeared to start as a localized tongue lesion, and it was not until some time later that dissemination was evident. At this time marked weakness, anorexia, and weight loss were noted despite a fever of but 100° F. It was not until 2 weeks before death that the blood pressure fell to 90/70. Therapy with adrenal cortical extract, and sodium chloride instituted at that time was ineffective.

The only symptoms presented by Case 2 which might have placed the adrenals under suspicion from the start were excessive weakness and fatigue which caused the patient to remain in bed for the 5 weeks prior to her admission to the Geisinger Hospital. Indeed her weakness was so severe that she was unable to stand long enough for the performance of the Romberg test. The peculiar cyanotic color of the skin may possibly also be attributable to the adrenal failure. Despite the complete adrenal destruction, however, a fall in blood pressure was not noted.

Of interest is the fact that in the cases of adrenal failure due to histoplasmosis (Table 2) a ratio of 2 males to 1 female is found. This is the same ratio noted in

Addison's disease from all causes.⁵ The age group (39 to 63) is somewhat older than that given for Addison's disease (30 to 50).⁶ All cases in the series belonged to the white race.

Although 76% of the cases of adrenal histoplasmosis showed caseation, only 28% of those of adrenal torulosis did. Although this series is too small to draw conclusions as to pathogenesis, it is interesting to note that the caseous reaction may be an allergic one,¹⁹ and that histoplasma capsulatum is capable of producing sensitization,⁸ while *Cryptococcus neoformans* frequently is neither antigenic, nor allergenic.¹¹

Tuberculosis and other granulomatous processes such as Hodgkin's disease have been observed to accompany both histoplasmosis and torulosis (Cases 1 and 6, Table 2). It is well known that the demonstration of tubercle bacilli in sections is often very difficult. For these reasons it has been suggested that many cases of both histoplasmosis and torulosis may be but the secondary invasion of yeasts in pre-existing tuberculous lesions—a concept which would explain the close similarity of the lesions found in the 3 diseases.

Summary. 1. Case reports available to us of adrenal involvement by *Histoplasma capsulatum* and by *Cryptococcus neoformans* (*Torula histolytica*) are reviewed.

2. Adrenal insufficiency due to massive destruction of the glands is a complication of both histoplasmosis and torulosis, being more common in the former.

3. To our knowledge, the first case of adrenal insufficiency due to torulosis and the ninth case due to histoplasmosis are herewith presented.

4. Excessive weakness appears to be the earliest symptom of adrenal destruction caused by these two diseases.

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ROENTGEN THERAPY IN TRAUMATIC MYOSITIS OSSIFICANS

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THE present study was undertaken in order to determine the efficacy of roentgen therapy in traumatic myositis ossificans. In the recent literature there are few reports of its use in this condition. Because of the excellent results obtained in the treatment of bursitis we were induced to try it in a series of patients with traumatic myositis ossificans. The rationale of employing this method in the treatment of myositis ossificans traumatica is believed to be on a sound basis, since the condition begins as an inflammatory reaction in response to hemorrhage produced by trauma.

Etiology. The terms myositis ossificans traumatica, ossifying hematoma and calcifying hematoma have been used interchangeably to describe the process of calcification and ossification occurring within muscle tissue in response to trauma. Although the condition tends to become asymptomatic and to regress, it may be accompanied by disability and discomfort for varying periods of time and may even be progressive. It occurs most commonly in young men. The initiating factor which is most frequently described in the recent literature is acute trauma. Particularly common sites of involvement are the muscles of the anterior aspect of the thigh following a blow, and the elbow region following dislocation. Less frequently the trauma is of chronic nature. Billroth (quoted by Geschickter¹) in 1885 described myositis ossificans traumatica under the term "rider's bone," since it occurred in the adductor muscles of the thighs of cavalrymen. Later a similar condition was described in the deltoid

muscles of infantrymen. In our series chronic irritation played a rôle in 1 case. However, the majority were in young men of college age who suffered injury while playing football, basketball, or participating in other sports. In 1 case myositis ossificans developed about the elbow joint following dislocation.

Pathology and Pathogenesis. A number of theories have been offered to explain the pathogenesis of myositis ossificans traumatica. Carey⁵ has summarized most of these theories as follows: (1) hemic, which maintains that hemorrhagic blood becomes organized and is transformed into cartilage and finally into bone; (2) sesamoid bone, according to which, trauma stimulates the development of sesamoid bones; (3) bone formation within muscle as a result of detached periosteal flaps; (4) subperiosteal dissemination, which holds that when periosteum ruptures it allows subperiosteal osteogenetic cells to proliferate and invade the musculature; (5) hematogenous infection; (6) synovial escape, which gives consideration to the possibility of synovia escaping into soft parts; (7) metaplasia of intramuscular connective tissue into bone; (8) combined metaplastic and periosteal theory; (9) underlying diathesis or dyscrasia. Another theory was added by Hirsch and Morgan,⁹ who believe that endochondral bone formation can take place as a result of stimulation of fibrocartilage by trauma. They find fibrocartilage to be a normal tissue constituent in areas where traumatic myositis ossificans occurs.

It is rather generally accepted that myositis ossificans begins as an inflam-

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matory process in response to hemorrhage due to tears and contusions of muscles, muscle insertions, periosteum and blood vessels. Thorndike¹⁸ logically outlined the pathogenesis as follows: (1) a severe deep muscle contusion accompanied by the tearing of muscle fibers and capillaries and loosening of periosteal cells, (2) hemorrhage with accompanying inflammatory reaction that one would expect in hematoma formation, and (3) hematoma absorption in which ossification takes place.

Histologically myositis ossificans has been studied in various stages and by various workers. Geschickter and Maseritz⁸ in analyzing 25 cases found the presence of hemorrhage, the organization of hemorrhage, myxomatous tissue, angiomatous tissue, calcification en masse, hyalinization of capillaries and degeneration of muscle; any combination of these findings were seen accompanying bone formation in a section or group of sections. Degeneration of muscle, hyperplasia of connective tissue and organization of hemorrhage were the earliest histological manifestations which they observed. They noticed a tendency to capsule formation which was simultaneous with calcification en masse in the inner portion of the young connective tissue. Islands of osteoid tissue which became invaded and surrounded by osteoblasts and marrow spaces were found later. With advancing bone formation they observed partially formed osteoid spicules and more completely formed spicules typical of those seen in the process of cancellous bone formation. Cartilage was present in about one-fourth of the instances. Geschickter and Maseritz⁸ felt that osteoblastic formation and calcification were the probable changes which preceded bone formation. Hirsch and Morgan⁹ saw acute exudative inflammation of the tissues and edema and hemorrhage in the early stages as a sequela of the trauma; in later stages they found scar-like connective tissue or granulation tissue with masses of bone and cartilage in varying amounts. Shipley,¹⁷

Pack and Braund,¹⁵ Butler and Woolley,⁴ and others have reported the development of malignant neoplasm in myositis ossificans.

In one instance in this series surgical removal of a 3 by 2½ inch calcified hematoma from the substance of the right vastus intermedius was done with subsequent recurrence. Histologically the removed mass showed areas of degenerating muscle surrounding an area of laminated bone and well formed bone spicules with marrow spaces composed of loose fibrous tissue infiltrated by lymphocytes and phagocytes filled with some blood pigment (Fig. 3).

Clinical Findings. The most constant symptom is pain which may be of short duration or persistent or progressive for varying periods of time. On the other hand pain does not necessarily accompany the appearance of myositis ossificans traumatica. Limitation of motion may result particularly when the site of involvement is near a joint or a muscle insertion. The earliest physical finding consists of a doughy swelling which increases in size and becomes more firm.

Roentgenographically, calcification may appear from 1 to 4 weeks after injury. Lewis¹² claims that bone formation reaches its maximum and ends within 6 weeks and then either regresses or remains stationary. Geschickter and Maseritz⁸ state that maximum bone formation occurs in 10 weeks to 20 months. Thorndike¹⁸ followed a series of 25 cases for a period of years to determine the final outcome of the ossification. Nine cases (36%) were found to have absorbed spontaneously. Some of these regressed as early as 2 months after their discovery, while another case showed only partial resorption in 5 years. Thorndike concluded that the criteria for absorption seem to be mainly size and location as well as individual diathesis. The smaller areas of calcification and those in the upper extremities, with the exception of those about the elbow, seem to have a greater tendency to disappear. Those in the belly of a muscle tend to

become dormant and painless even in severe cases when regression is incomplete. Those near muscle insertions may become dormant but tend to interfere with function. Hobart¹⁰ believes that continued irritation as by movement will tend to make the process progressive.

In our series of cases pain was present in all and usually it was the chief symptom which led the patient to seek medical advice. Limitation of motion was the chief complaint in a few and was associated with pain to some extent in all. The duration of symptoms varied from 2 weeks to 1 year. Soft tissue swelling and roentgenographic findings were present in all patients.

Treatment. The prophylactic measures most widely advocated are the avoidance of massage, the application of cold and the use of a compression bandage immediately after an injury, thus attempting to reduce hemorrhage. Böhrer³ goes so far as to say that he believes myositis ossificans traumatica occurs as the result of massage following an injury rather than of the injury itself. Thorndike¹⁸ states that evacuation of a hematoma in its early stages is contraindicated.

Treatment of myositis ossificans traumatica after calcification has occurred has consisted of physical therapy and surgical removal. Early surgical removal has been condemned because of the tendency of the lesion to recur. Thorndike¹⁸ recommends operative removal only in those cases where ossification occurs near a joint or in the origin or the insertion of a muscle, or where function is permanently impaired, and then only from 12 to 24 months after injury.

The use of Roentgen rays for the treatment of myositis ossificans has been described by Jüngling¹¹ and others.^{1,2,13,14,16} Chevrrier and Bomriot⁶ have treated dislocation of the elbow prophylactically with Roentgen rays on the theoretical basis that inflammatory processes would be influenced and the myositis ossificans therefore prevented. The beneficial action of prophylactic Roentgen therapy is difficult

to prove for the obvious reason that many unirradiated sites of injury will not become involved with myositis ossificans. Jüngling¹¹ treated with Roentgen rays early cases in which the inflammatory process was likely to be still present. He believed that results could not be expected in a permanent inactive process which causes only limitation of mobility of a joint but that Roentgen therapy might still be used during the first 3 months for the reason that during this time there are still inflammatory changes present.

The technique employed in the use of Roentgen rays in treating the patients of our series consisted of doses of 150 r to 200 r (in air) delivered to 1 or 2 fields daily or every other day for 3 or 4 treatments. When indicated, a second series was given in 4 to 6 weeks and a third in 2 to 4 months after the first course. In 5 cases, only 1 course was necessary. In the other 5 cases 2 or 3 courses were given. Technical factors were 175 or 400 kv., 50 cm. FSD and half value layers of 1.05 mm. Cu. and 2.4 mm. Cu. respectively. The field size was large enough to include a wide zone about the area of calcification.

Results. The accompanying Table 1 outlines the significant clinical and roentgenographic findings and the results of Roentgen therapy in each of the 10 cases. Complete relief of pain occurred in all cases following treatment to the area involved by traumatic myositis ossificans. Relief of pain was noted within 4 to 6 weeks following Roentgen therapy. Often the improvement was dramatic and began as soon as 2 or 3 days after treatment. The following case illustrates this.

Case Reports. CASE 1. W. W., a police officer, age 34, was first seen on Nov. 16, 1944, at which time he complained of an exquisitely painful lump "as sore as a boil" on the posterior aspect of his left thigh. The pain had begun 6 months previously and had become progressively more severe. He had no history of acute injury. However, his duties included riding in a squad car a good portion of the day. Considerable aggravation of the pain resulted when he shifted

TABLE 1.—CLINICAL DATA IN 10 CASES OF TRAUMATIC MYOSITIS OSSIFICANS

Name	Age	Site	Etiology	Symptoms	Duration	Roentgenologic findings	Therapy	Symptomatic results	Roentgenologic results
D. F.	20	Lt. elbow	Dislocation	Severe pain and marked limitation of motion	3 mo.	Calcification, ossification in periarticular soft tissue lateral to elbow joint and lower end of humerus	3 courses 3 x 200 r lat. elbow	Complete pain relief and improved motion within 4 wks. but persistent flexion deformity	60 % decrease in size after first course, slight further decrease following subsequent courses.
K. P.	22	Ant. rt. thigh	Injury	Pain and limitation of motion	3 mo.	Calcified mass in ant. aspect of rt. thigh	3 x 150 r ant. rt. thigh	Complete pain relief and increased motion within 4 weeks	No decrease in size but increased density.
K. D.	22	Antero-lat. rt. thigh	Recurrence after surgical removal	Marked limitation of motion and pain	2 wks.	Calcification in soft tissue anterior to shaft of rt. femur	2 courses 3 x 150 r 4 x 200 r	Complete pain relief and considerable increase in motion within 6 weeks	Slight decrease in size of calcification which became denser.
J. Z.	18	Lt. thigh	Basketball injury	Pain and limited motion	4 wks.	Laminated calcification in soft tissues along the lateral side of the mid shaft 8 cm. long	3 x 150 r.	Complete pain relief and return of motion to normal within 4 weeks	Complete absorption of calcium within 4 wks. after treatment.
T. T.	19	Lt. shoulder	Surfboard injury	Persistent, progressive pain	1 yr.	Seminilar shaped calcification below and ant. to glenoid fossa	2 courses 3 x 150 r A/p lt. shoulder	Complete relief of pain within 6 weeks	Slight absorption of calcium.
R. M.	16	Quadriceps lt. thigh	Injury	Severe pain	3 mo.	Calcified mass in soft tissues in ant. rt. thigh 17 by 7 cm.	4 x 150 r ant. thigh	Complete pain relief within 4 weeks	Decrease in size and more bony appearance of calcification.
R. F.	16	Quadriceps rt. thigh	Toboggan injury	Pain	3 wks.	Calcification in soft tissues ant. to shaft of femur 2.5 cm. long	2 courses 3 x 200 r ant. thigh	Complete relief of pain within 4 weeks	Complete absorption of calcium within 6 months.
J. L.	20	Ant. lt. thigh	Football injury	Pain	4 wks.	Calcification in soft tissues anterolat. to mid shaft of femur 3 by 6 cm.	3 x 150 r	Complete relief of pain within 6 weeks	Moderate decrease in size of calcification.
W. W.	34	Post. lt. thigh	Chronic irritation associated with occupation	Very severe pain and tenderness	6 mo.	Calcification posterior to shaft of lt. thigh 2.5 cm. in diameter	3 courses 3 x 150 r	Complete relief of pain within 4 weeks	Decrease in size of calcification.
D. R.	18	Ant. rt. thigh	Basketball injury	Pain	2 mo.	Laminated calcification soft tissues in anterolat. rt. thigh 5 by 15 cm.	2 courses 3 x 150 r	Complete relief of pain within 6 weeks	Reduction in size of calcified mass by one-third.

gears in his car. On examination a hard tender mass was found on the posterior aspect of the left thigh. Roentgenograms showed a rounded irregular calcific density, measuring approximately 5 cm. in length, in the soft tissues of the posterior aspect of the left thigh at the junction of the middle and upper third of the femur and having the appearance of myositis ossificans (Fig. 1, A). On 3 consecutive days he received 150 r (in air) to the affected region. Technical factors were 400 kv., 5 ma., 50 cm. FSD, HVL= 2.4 mm. Cu. Improvement began

was apparently due to mechanical interference resulting from the abnormal calcification and ossification within the muscle tissue. In these cases improvement of function usually lagged behind pain relief and as a rule a second or even a third course of therapy was given. In all but one, in whom a flexion deformity persisted, considerable or complete improvement of motion followed one or more courses of Roentgen therapy. The following case is of interest from several

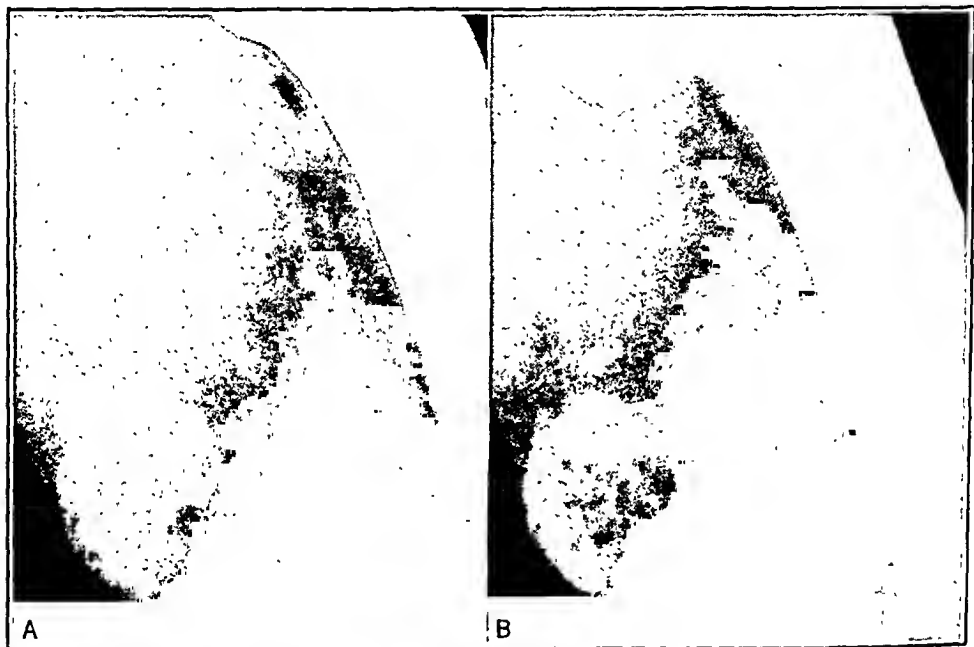


FIG. 1.—A, myositis ossificans traumatica before beginning Roentgen therapy; B, approximately 3 months after treatment with Roentgen rays. (Case 1.)

2 or 3 days following treatment. At the end of 4 weeks all pain had disappeared and on roentgenographic examination the calcified mass was found to be reduced to about two-thirds its original size. A second and third series were given at a 4 and an 8 week interval. Roentgenographic evidence of further reduction in the size was observed about 3 months after the first examination (Fig. 1, B). Symptoms have not recurred.

Limitation of motion was associated with pain to a lesser or greater extent in all cases. When pain was relieved, function usually returned promptly to normal. However, in 4 cases a limitation of motion

points of view, but particularly because of the improvement of marked limitation of motion.

CASE 2. K. D., a 22 year old white male, fell on Dec. 23, 1938, and struck the anterolateral aspect of the lower portion of his right thigh against an iron bar. Swelling and pain followed and persisted. His family physician prescribed hot and cold applications and elastic bandage, and 3 weeks later he aspirated hemorrhagic fluid from the site of injury. On Feb. 4, 1939, the patient was first seen in the Orthopedic Department of The State of Wisconsin General Hospital. He complained of pain in the right thigh and

limitation of motion in the right knee joint. On examination a hard, fixed, tender mass measuring 5 inches in length was found along the anterolateral aspect of the lower third of the right thigh. Flexion of the right knee was limited to 30° both actively and passively, neither could he completely extend his leg. Roentgenographic examination showed a considerable amount of calcification in the soft tissues anterior to the junction of the middle and lower thirds of the shaft of the right femur and having the appearance of myositis ossificans (Fig. 2, A).

to 120° . On Feb. 12, 1939, a roentgenogram showed that the calcified mass had been removed completely (Fig. 2, B).

On March 1, 1939, the patient returned again with flexion at the knee joint limited to 40° and inability to completely extend the leg. Pain was slight to moderate. A roentgenogram showed recurrence of the myositis ossificans (Fig. 4, A). Between March 1 and March 4, he received a course of Roentgen therapy consisting of 3 times 150 r (in air) to the involved area. Technical factors were 175 kv., 50 cm. FSD and HVL

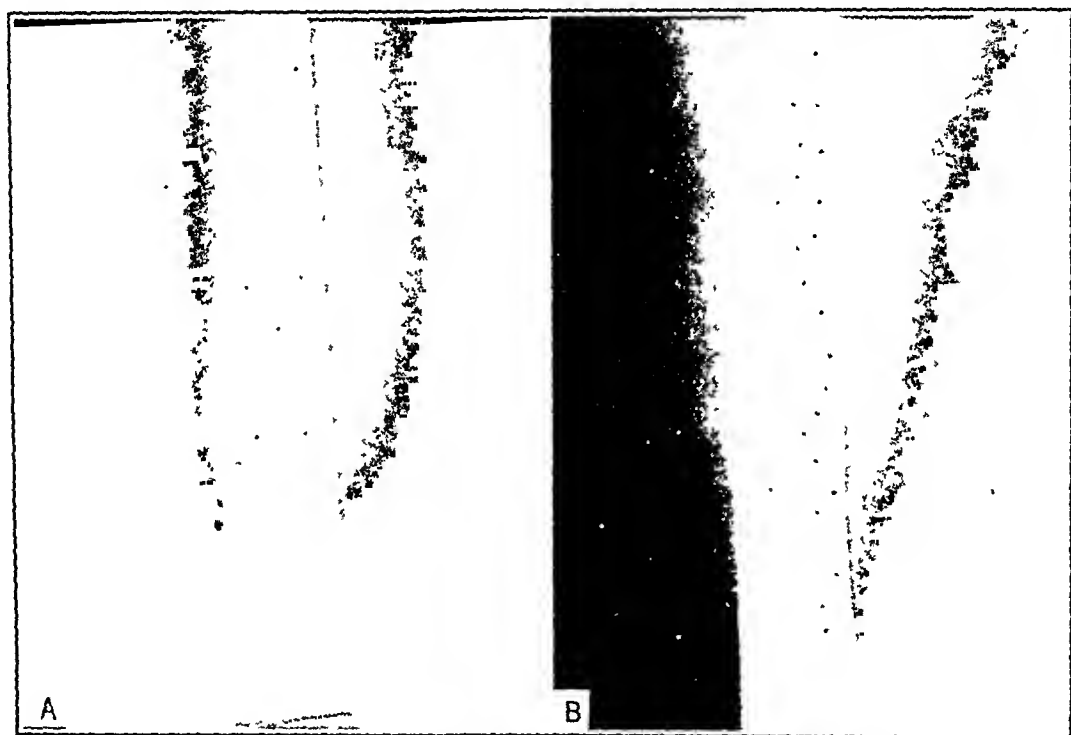


FIG. 2.—A, myositis ossificans traumatica before treatment; B, after surgical removal. (Case 2.)

The patient was referred to us on Feb. 9, 1939, for Roentgen therapy. After the second treatment, however, the surgeons decided to remove the calcified mass and consequently the course of Roentgen therapy was not completed. The microscopic study of the removed tissue showed degenerating muscle surrounded by an area of laminated bone. The bony spicules were well formed and the marrow spaces were composed of loose fibrous tissue infiltrated by lymphocytes and phagocytes filled with blood pigment. The histological diagnosis was myositis ossificans (Fig. 3). Under anesthesia before surgical removal flexion was limited to 40° ; after removal it was increased

of 1.05 mm. Cu. Five weeks later on April 20, his ability to flex the right knee had increased from 40° to 120° . Pain was present only when pressure was applied over the area. Roentgenograms showed a slight decrease in the size of the calcification. A second series of 4 times 200 r, using the same technical factors, was given. Further symptomatic improvement occurred and there has been no recurrence of symptoms to our knowledge. Roentgenograms on June 6, 1939, showed a smoothing of the area of calcification and a general increase in density but no resorption of calcification or extension of the process (Fig. 4, B).

Comment. Follow-up roentgenograms were obtained in all cases. In 2 cases the calcifications were completely absorbed. In one instance the absorption took place within 4 weeks after Roentgen therapy and within 2 months after the injury, and in another instance absorption took

consistently noted in roentgenograms taken after therapy had been administered. However, since it is well known that spontaneous absorption and decrease in size of myositis ossificans does occur, the described roentgenographic findings cannot necessarily be attributed to irradiation.



Fig. 3.—Photomicrogram of the surgically removed tissue. (Case 2.)

place within 6 months after treatment and within 7 months after the injury. It is noted that in these 2 cases treatment was given within 4 weeks after the trauma. With the exception of one case, at least a slight decrease in the size of the calcified area was observed. An increased density and a sharper and smoother outline was

tion. Symptomatic improvement could not definitely be associated with the amount of decrease in size of the mass.

Although the results of treatment are difficult to evaluate, particularly in a small group of cases, because of the tendency of myositis ossificans to regress and become inactive, beneficial results in this series of

cases appeared to be definitely related to treatment with Roentgen rays. Since half of the patients had symptoms which were persistent or progressive for at least 3 months, it is unlikely that the prompt symptomatic relief which occurred following Roentgen therapy happened to coincide with what might have been spontaneous regression. Most convincing in this respect is Case 2, in which the signs and symptoms of myositis ossificans recurred

toms are of long duration. Since traumatic myositis ossificans can be very disabling to otherwise healthy young men and since the only other adequate method of treatment is surgical and is often followed by recurrence, particularly if done in less than a year following the onset, we believe that the beneficial results obtained in this group of cases justify further trial of Roentgen therapy in myositis ossificans traumatica.

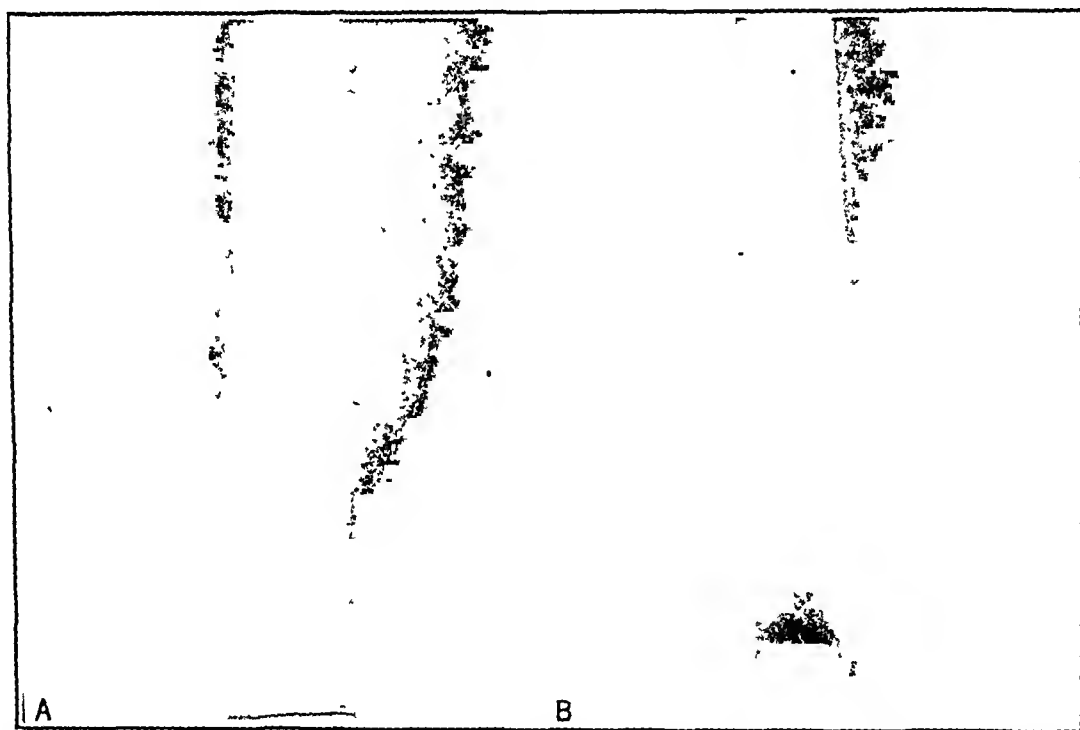


FIG. 4.—A, recurrence 2 months following operation; B, approximately 3 months following Roentgen therapy. (Case 2.)

following surgical removal, yet after treatment with Roentgen rays complete relief of pain and considerable increase of motion resulted. The action of Roentgen rays in myositis ossificans traumatica is believed to be similar to that in chronic bursitis and other inflammations. As in bursitis, it is likely that the earlier in the course of the disease treatment is given the better the results will tend to be. When symptoms of pain and limitation of motion persist or are progressive, it undoubtedly indicates that inflammatory changes are still present and consequently, improvement may be expected even where symp-

Summary. 1. A brief review of the literature concerning the etiology, pathology and pathogenesis of myositis ossificans traumatica is given.

2. Ten cases of symptomatic myositis ossificans traumatica treated with Roentgen rays are presented.

3. Following Roentgen therapy complete relief of pain resulted in all cases. Limitation of motion was markedly improved or restored to normal in all but one in which only slight to moderate improvement of function was obtained.

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THE PARATHYROID: A STUDY BASED, IN PART, ON SIXTY POST-MORTEM EXAMINATIONS WITH PRESENTATION OF A CASE OF HYPERFUNCTIONING ADENOMA*

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THE history of the part played by the parathyroid in disease does not go far. In 1864 Engel described a case of unusual bone disease which von Recklinghausen⁴¹ in 1891 classified with certain of his cases as generalized fibrocystic osteitis and distinguished them from osteomalacia.

As far as one can be certain, the parathyroid was not recognized as an independent anatomic structure until 1880 when the Swedish anatomist, Sandstrom, described the gland and gave it its name. So far as its function is concerned, nothing definite was known until 1891 when the French physiologist, Gley²⁸ showed that in dogs extirpation of the parathyroid gland led to characteristic manifestations of tetany.

In 1902 Benjamins¹⁴ reported the first case of parathyroid tumor, probably an adenoma. In 1903 Erdheim²⁵ reported a case which has been recorded in the literature as being the first. However, he refers to the case of Benjamins. Askanazy¹¹ in 1902-04 published the results of an autopsy of a patient who had suffered from generalized decalcification and found a parathyroid tumor. Later Erdheim drew attention to the relation between the parathyroid and the skeleton. He noted the association between bone disease and enlargement of the parathyroid gland and concluded that this enlargement might be encountered as a consequence. His failure to recognize the etiologic significance of a

parathyroid tumor in generalized osteitis fibrosa cystica no doubt retarded progress in the field. In 1925 Mandl,³⁵ through courage, for the first time removed a parathyroid tumor in a case of bone disease and led the way for other surgeons.

Since 1930 better understanding of hyperparathyroidism and its clinical manifestations has been due largely to the works of Albright and his associates.^{1,2,3,4,5,6,7,8} They showed that renal disease was a more common manifestation and that hyperparathyroidism could occur and be recognized in cases in which there was no evident bone disease.

The insidious manner in which a hyperfunctioning parathyroid adenoma exacts its toll over a period of years is well shown in reports from the literature. Only among those clinicians who are alert to its manifold manifestations along the way will early diagnosis be made. The removal of the tumor will cure the disease but the effects of irreparable kidney and bone damage which come about in the late stages may leave little room for rejoicing to either the surgeon or the patient as to the results.

In approaching the subject for this study, the parathyroid gland was studied from various aspects with the plan in mind to portray as clearly as possible certain facts which might be of help to the surgeon. Microsections, made from each of the 60 postmortem dissections, were

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studied with respect to the age of the patient and the anatomical diagnosis.

EMBRYOLOGY.^{10,12,21} The primitive pharynx is the source of numerous organs. Most of the developmental complexities occur during the transitional period when the embryo passes from a stage in which the pharynx is arranged for branchial respiration to the stage in which breathing is anticipated. The branchial arches are bar-like ridges separated by grooves which appear on the lateral surfaces of the embryonic head. In the human there are 5 arches separated by 4 external ectodermal grooves. Subjacent to these grooves, the entoderm of the pharynx bulges outward to constitute complimentary pharyngeal pouches. There are 5 sets of pouches, the last being rudimentary and attached to the fourth. The pharynx becomes flattened dorsoventrally and broadened at its cranial end, as a result of which it is triangular in outline. Each typical pouch develops a dorsal and ventral wing.

The inferior parathyroid glands develop from the dorsal wings of the third pharyngeal pouches. They are set free from the pharynx and drawn down by the migrating thymic primordia which develop from the ventral sacculations of the third pharyngeal pouches.

The superior parathyroid glands develop from the dorsal wings of the fourth pharyngeal pouches. Presumably the lateral thyroid primordia develop from the ventral wings of the fourth pouches. However, the main mass of the thyroid develops from the ventral floor of the pharynx from an entodermal pocket forming in the midplane at the level of the first pharyngeal pouches.

As schematically shown in Figure 1, the extent of migration of the superior and inferior parathyroid glands and any relation they may bear to the thyroid and thymus glands may be realized. Parathyroids IV (superior) descend a relatively shorter distance and are usually in close relation to the thyroid gland. Parathyroids III (inferior) descend a relatively greater distance and may be in relation to

the thymus. They usually come to rest opposite the lower pole of the thyroid but may extend into the mediastinum or be invested within the capsule of the thymus.

ANATOMY. In these dissections the superior pair were more often found closely applied near the lateral margin posteriorly just above the middle of the body of the thyroid gland. The inferior pair were more often located just below and lateral to the lower pole of the thyroid embedded in loose areolar tissue. (Fig. 2.) On finding one gland, its mate was found ordinarily in a corresponding position.

The weight for each has been given as 0.035 gm., average. Because of their extreme softness, the shape and apparent size varies. Each measures 6 to 7 mm. x 3 to 4 mm. x 1.5 to 2 mm.³⁶ Most commonly they are flattened, ovo-elliptical structures. In this study the superior gland was usually found to be smaller, flattened, and irregular due to pressure of contiguous structures. Each was contained in a thin filmy capsule. It was not possible always to identify the gland by its color. Usually it was of a putty tan shade. Some had a pink cast like thyroid tissue, and others were grayish-yellow. Occasionally a distinctly brown shade existed. A small blood vessel was seen to branch over the surface of the gland in about 10% of the cases. At times the only means of identifying the gland grossly was by teasing the surface with a needle which brought out its filmy encapsulated form and its soft consistency.

Experience with dissection of the neck has shown that one can identify grossly the parathyroids. However, because of their variation in position they are not always easy to find. They have to be distinguished from: (1) a loosely attached peripheral bud of thyroid tissue (deeper reddish cast identical to that of adjacent thyroid with a firmer consistency); (2) lymph node (usually round, darker in color, and of brittle hardness); (3) encapsulated fatty tissue (soft but of a very pale yellow color); and (4) aberrant thymic tissue which is enveloped by membranous

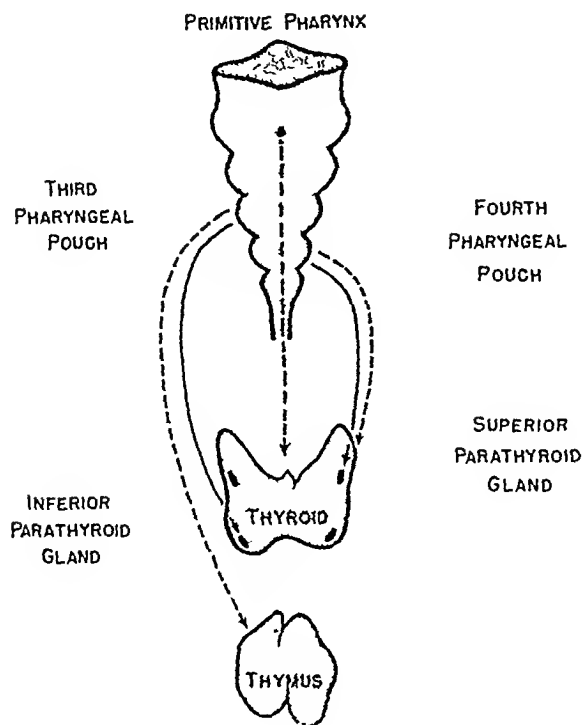


FIG. 1.—Embryology. Descent of the parathyroid glands showing relation to the thyroid and thymus. The inferior parathyroids and thymus take origin from the third pharyngeal pouches, as shown on the left side of the diagram. The superior parathyroids and lateral thyroid bodies take origin from the fourth pharyngeal pouches, as shown on the right side. The main mass of the thyroid develops from the ventral floor of the pharynx about the level of the first pharyngeal pouches. The wider range for the location of the inferior glands along with their possible relation to thymus is appreciated.

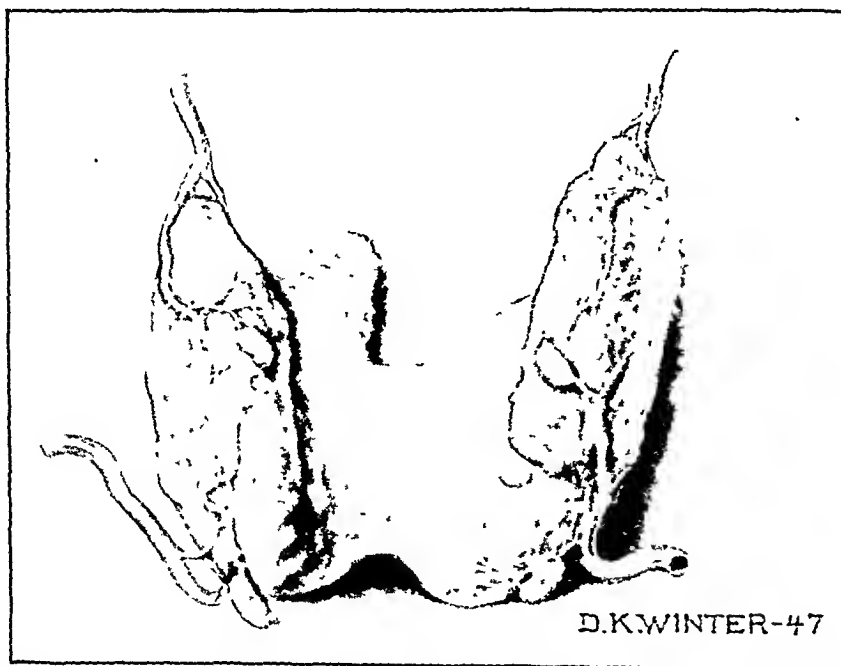


FIG. 2.—Anatomy. Tracheal surface of the thyroid gland to show the 2 pairs of parathyroids as they are often found at necropsy. The blood supply usually is derived from the inferior thyroid arteries.

septa of connective tissue (soft with a pale, dirty grayish-yellow appearance).

HISTOLOGY.^{13,17,18,36} The study of the histology of the parathyroid gland in these cases was made on patients whose ages at time of death ranged between 21 and 82 years.

The gland is supported by a thin capsule. Connective tissue strands pass into its substance forming delicate septa. The blood supply, which is rich, most often comes from the inferior thyroid vessels. A vascular twig enters at one point, divides under the capsule, and spreads out along the septa. The nerve supply is scanty and the fibers are thought to be entirely vasomotor.

The parenchyma is composed of anastomosing cords of cells between which the capillaries are located. Often the cells are disposed as continuous masses. Less commonly they form acini of various sizes which may contain colloid-like material. Varying numbers of fat cells are usually scattered among the epithelial cells.

The chief or principal cell makes up the bulk of the gland. It is polyhedral in shape and poorly outlined. The cytoplasm is usually scant and faintly acidophilic. Unstained areas, especially about the nucleus, sometimes give the appearance of vacuolation, and these cells have been termed transitional. The nucleus is round and sharply demarcated by a basophilic outline. It is large, comprising more than half the cell volume. Chromatin usually is abundant.

Occasionally the cytoplasm appears to be entirely absent, *i. e.*, complete vacuolation. This cell is termed "water clear" (wasserhelle). It is sharply outlined and larger than the chief cell. The nucleus is usually more hyperchromatic and eccentrically located. It may occur singly among transitional cells or in groups.

The oxyphil cell is said to appear after puberty, and to increase in number with advancing age, forming large islands which are sharply outlined but not encapsulated. It is polyhedral in shape with a well defined cell margin and is larger than the

chief cell. The cytoplasm is uniformly reddish-pink and usually completely fills the cell. The nucleus is about the size of the chief cell but not so hyperchromatic. In this study the cell was seldom seen to occur singly. The islands were usually located subjacent to the capsule or close to the connective tissue stroma. The dark oxyphil cell as described by Castleman and Mallory¹⁷ was not observed. Best Carmine stain was used in some instances to demonstrate glycogen which was found to be present in the chief but not in the oxyphil cells.

In a few areas the acinous nature was so marked that it simulated the structure of the thyroid gland. In some sections thymic tissue was found attached to parathyroid tissue, and cord-like buds of chief cells were seen extending into the lymphoid stroma. The appearance was such that it suggested a close relation might exist at some time between the epithelial cells of the Hassall's corpuscles and the epithelial cells of the parathyroid.

PATHOLOGICAL PHYSIOLOGY. The parathyroid hormone acts chiefly upon the metabolism of calcium and phosphorus and apparently regulates the level of calcium ions. There is some evidence that the stimulus for the parathyroid glands to produce more hormone is a serum calcium ion level below normal.

No unanimity has been reached about the mechanism by which hyperparathyroidism leads to the changes in bone and to the typical biochemical syndrome. Collip and others believe that the hormone has a specific action on bone tissue, causing, notably, proliferation of osteoclasts which in turn lead to resorption of bone and perhaps the formation of giant cell tumors.^{31,46} Excessive amounts of calcium and phosphorus are liberated from the skeleton and transported by the blood to the kidneys and intestines. In this way the hypercalcemia, as well as the excessive amount of calcium and phosphorus in the urine can be explained. Why the inorganic phosphorus content of the blood diminishes under the circumstances is not clear.

It is Albright's contention^{1,3} that hyperfunction does not act primarily upon the skeleton but first influences the phosphate metabolism. He believes the hormone lowers the renal threshold for the excretion of phosphorus in the urine and thereby increases the phosphorus output. This is attended by fall of the inorganic phosphorus and a rise of calcium in the serum. The urinary calcium first decreases and then increases. The decrease of the phosphate ions in the serum, resulting in un-

phorus compounds of the blood. The concentration is a measure of disease of bone and not of hyperparathyroidism. Where there is little or no bone involvement its value is normal. In osteitis fibrosa cystica of von Recklinghausen, in which proliferation of osteoblasts and new formation of bone is constantly present, the phosphatase content of the blood is increased.

CLASSIFICATION OF DISEASES OF THE PARATHYROID GLANDS. Clinically significant diseases of the parathyroid glands de-

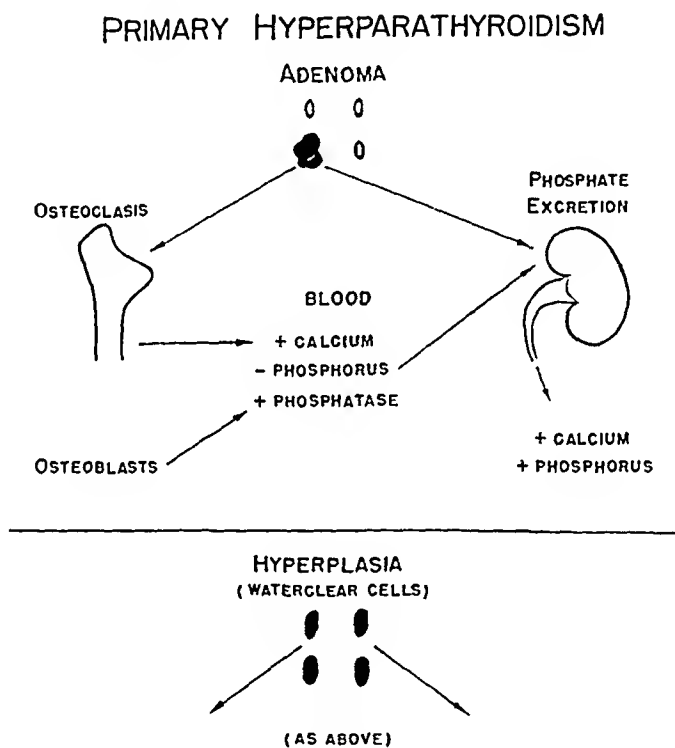


FIG. 3.—Primary hyperparathyroidism. Scheme to show the characteristic biochemical changes when due to an adenoma or to hyperplasia, and the mechanism by which they occur. Collip believes that the hormone has a specific action on the osteoclasts which resorb bone tissue and leads to hypercalcemia. Albright believes that its action is first on phosphate metabolism. The renal threshold for the excretion of phosphorus is lowered, and the effect on calcium metabolism is a sequella.

saturation of the blood with calcium phosphate, ultimately leads to liberation of the calcium phosphate of the bones. The influence of the hormone on calcium metabolism and on the bones would then be only a sequella of the change of phosphorus metabolism. Not all the investigations give confirmatory evidence to this view.

The serum alkaline phosphatase is apparently derived from osteoblastic tissue.¹⁵ It is an enzyme capable of liberating inorganic phosphorus from the organic phos-

pend on whether there is too much or too little of the hormone produced, and may be classified simply under three headings:

1. PRIMARY STATES (other than neoplasms where no cause has been found). From 1934 to 1947, 26 cases of hyperplasia with hyperfunction have been reported.^{5,16} In each instance all of the glands were involved and were composed entirely of water clear cells. Chronic idiopathic hypoparathyroidism, in which there is atrophy

of the parenchyma with fat replacement, is equally as uncommon.

2. **SECONDARY STATES.** Physiopathologic conditions resulting in chronic renal insufficiency with phosphate retention and chronic acidosis, and diseases which deplete the available calcium in the body (rickets, osteomalacia, multiple myeloma, carcinomatous metastasis to bones, etc.) can cause hyperplasia of the chief cells

involves one gland. However, in about 8% two separate adenomas have been found. In the hyperfunctioning tumors, the chief cells are responsible. Adenomas consisting of oxyphil cells have not been shown to produce hyperparathyroidism. These cells have no known function.

Hyperfunctioning tumors giving unequivocal clinical evidence of malignancy are exceedingly uncommon. In rare in-

SECONDARY HYPERPARATHYROIDISM

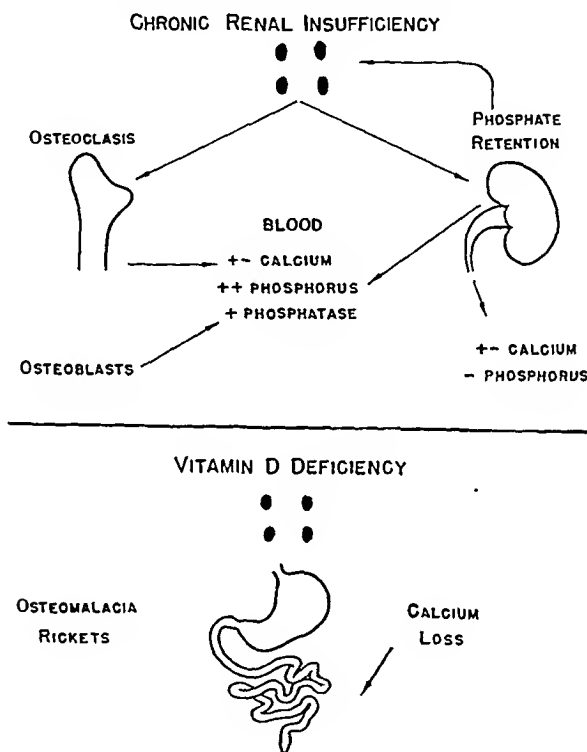


FIG. 4.—Secondary hyperparathyroidism. Scheme to show the biochemical changes and the mechanism by which they occur. In chronic renal insufficiency the stimulus to overactivity of the gland apparently results from phosphate retention. In osteomalacia and rickets, the stimulus is a calcium deficit in the blood stream.

with enlargement and hyperfunction of the parathyroid glands as a compensatory measure. Hypofunction, which may result in tetany, will occur when there has been sufficient injury to or excision of parathyroid tissue during thyroidectomy.

3. **NEOPLASMS.** In 1902 the first case with reliable evidence of an adenoma was published;¹⁴ reports of cases through 1946²⁷ have mounted to 337. Usually the tumor

stances have they been shown to recur, invade, or metastasize.^{9,27,29,30,38} There have been confusing reports of non-functioning malignant parathyroid tumors.

CLINICAL MANIFESTATIONS OF HYPERPARATHYROIDISM. The clinical manifestations of hyperparathyroidism are protean and most variable. The way in which the disease becomes evident may be shown by

its effect upon the circulating blood, the urinary tract, and the skeleton.

1. Blood (increased calcium—decreased neuromuscular excitability): Apathy, weakness, fatigue, anorexia, nausea and vomiting, constipation, weight loss, bradycardia, cardiac irregularities, and conduction defects.

2. Urinary Tract: Increased calcium and phosphorus excretion attended by thirst and increased urine output; renal calculi with resultant symptoms; and renal damage from calcium deposits in the parenchyma, pyelonephritis or obstruction with evidences of insufficiency.

3. Skeleton (demineralization and osteoclasia): Pain and tenderness of bone, pain on weight bearing, pathological fractures, deformities, decrease in height, cysts, tumors, epulides.

The full range of symptoms is to be encountered only in a case of severe "classical" osteitis fibrosa cystica, and even then there is marked variation in their occurrence and severity. In most cases the history has disclosed that the patient has had the disease years before the diagnosis was made.

Except in instances of severe hypercalcemia, symptoms may be vague, and in cases in which there is minimal alteration of the chemistry of the blood they are often absent. Since the chemical alterations are the reverse of those encountered in parathyroid tetany, one would expect to encounter symptoms which represent the converse of tetany, *i. e.*, decreased neuromuscular irritability. This is, indeed, the case. Occasionally, gastrointestinal symptoms, such as attacks of abdominal pain, nausea and vomiting, are the predominant features.

The excessive loss of minerals is accompanied in most instances by conspicuous polyuria and polydipsia which has led to a mistaken diagnosis of diabetes insipidus. Polyuria is not always present and its presence or absence cannot be correlated with the degree of calciuria which exists.

In a high percentage of cases, symptoms

associated with nephrolithiasis are the first manifestations of the disease. Calcium salts may be deposited also in the pyramids (nephrocalcinosis) and lead to renal insufficiency. The diffuse calcification of the renal parenchyma, associated with fibrosis and destruction of renal substance, leads to irreversible changes even though the hyperparathyroidism is eliminated. It may be difficult to distinguish clinically primary hyperparathyroidism with osteitis fibrosa cystica and secondary urinary insufficiency, from primary renal disease with accompanying secondary hyperparathyroidism and renal osteitis fibrosa cystica. The distinction is important, for, in the case of primary disease, removal of the parathyroid tumor may prolong life, whereas it is probable that, in primary renal disease with secondary hyperparathyroidism, parathyroidectomy would shorten life.

In many cases in which the absorption of calcium from the diet is approximately equal to that lost through the urine, no evident change occurs in the skeleton. In other cases, there may be any degree of skeletal involvement. Patients with minimal changes may have no symptoms whatever, or, at the most, have vague aching and pain. When involvement is more marked, pain and tenderness of bones and especially pain on weight bearing are presenting symptoms. Any bone tumor which on biopsy turns out to be a benign giant cell tumor (osteoclastoma) may be evidence of underlying hyperparathyroidism. Such a tumor of the jaw is called an epulis; it is present in an appreciable number of cases, and might direct the attention to the underlying disease. Not every epulis, however, is due to hyperparathyroidism. A pathological fracture sometimes is the first clue to the disease.

The differential diagnosis has consisted largely in distinguishing hyperparathyroidism from other conditions which produce hyperecalcemia and from diseases affecting the skeleton in a similar manner. Essential laboratory data in arriving at the diagnosis in a given case should in-

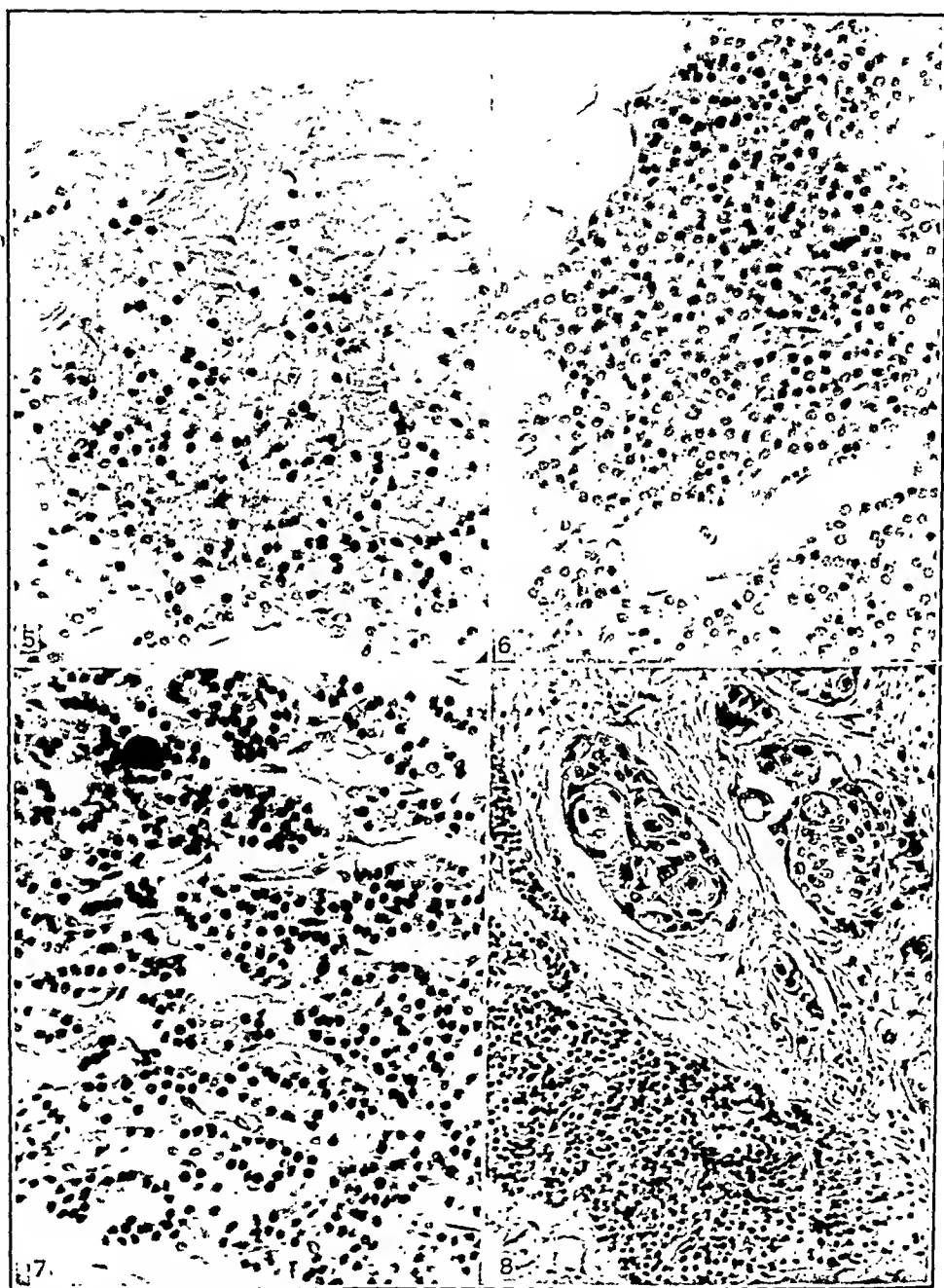


FIG. 5.—The parathyroid gland from a patient (CASE 1) with severe chronic arthritis deformans. Water-clear cells and hyaline degenerative changes are seen. ($\times 350$.)

FIG. 6.—The unirradiated left parathyroid gland (CASE 2). Fat cells are seen in the stroma. ($\times 350$.)

FIG. 7.—The irradiated right parathyroid gland (CASE 2). The chief cells are shrunken and their nuclei tend to be hyperchromatic. Fat cells are absent. There is fibrosis about the cords. ($\times 400$.)

FIG. 8.—The irradiated right parathyroid gland (CASE 2). Nests of epidermoid carcinomatous cells are seen in lymphatic channels. ($\times 250$.)

clude: repeated determinations of serum calcium and phosphorus, serum proteins, non-protein nitrogen, carbon dioxide combining power, and serum alkaline phosphatase when there are bone changes.

Histopathology. CASE 1. Degenerate parathyroid gland showing only water clear cells.

In Figure 5 is shown the histopathological findings in the parathyroid removed from a patient (J. C.), age 50 years, who for 9 years had been unable to walk because of severe arthritis deformans involving all major joints. He had been cared for in the Veterans Hospital for $8\frac{1}{2}$ years before death and was found also to have renal calculi with evidence of kidney damage. Roentgenographs of the bones disclosed generalized osteoporosis. Serum calcium and phosphorus levels were within normal limits. The serum alkaline phosphatase was elevated. The N.P.N. rose from 35 to 100 mg. during the last year of life.

At necropsy, the kidneys were found to be badly damaged. Only one pale yellow parathyroid gland, of normal size, was found. It consisted entirely of water clear cells with scattered fat cells. There were marked hyaline degenerative changes in the subcapsular region, between the lobules, and around the arterioles.

CASE 2. Effects of irradiation therapy and metastasis of carcinoma to right parathyroid.

In the case of A. J., the effects of irradiation on the parathyroid gland can be seen (Figs. 6, 7, 8). The patient was a 62 year old male who was admitted to the hospital for treatment of bronchogenic carcinoma with cervical metastasis. He was given palliative irradiation over a period of 1 month, consisting of 1950 R units to each the anterior and posterior mediastinum and 3000 R units to the right side of the neck. The left side of the neck was not irradiated. Postmortem examination showed the right lobe of the thyroid to be replaced by carcinoma. A soft, pale tan parathyroid gland, $6 \times 2 \times 2$ mm., was on the anterolateral surface of the metastatic tumor mass to which it was loosely attached. The left lobe of the thyroid was uninvolved, except for a metastatic nodule in the lower pole. A normal-sized parathyroid gland with slightly

darker color was located just below the left inferior pole.

Histologically, the left parathyroid gland showed a predominance of chief cells. There were several acini, two of which were moderately large and contained colloid-like material. Two small islands of oxyphil cells were present and fat cells were scattered throughout. The right gland (irradiated) showed shrunken chief cells with increased fibrosis about the cords. There were no oxyphil or fat cells. Nests of epidermoid carcinomatous cells were present under the capsule and in the lymphatic channels.

CASE 3. Minute oxyphil adenoma.

The photomicrograph shown in Figure 9 was made from a patient (A. H.), age 57 years, who died from a brain tumor. A review of the clinical studies disclosed no evidence suggesting hyperparathyroidism. Serum calcium and phosphorus were not determined.

The parathyroid glands grossly appeared normal. However, one gland disclosed on section a well circumscribed adenoma ($1\frac{1}{2} \times 1$ mm.), consisting of pale oxyphil cells. Some of these cells contained vacuoles and one small acinus with colloid material in it was noted. The surrounding chief cells were compressed and arranged in cords.

CASE 4. Hyperfunctioning parathyroid adenoma; report in detail.

W. J. U., a white Spanish American War veteran, age 70 years, was admitted to the Veterans Hospital, Hines, Ill., May 28, 1946, for the treatment of "probable carcinoma of the descending colon." He died 3 months later.

History. Members of the family lived to be old. There was no record of cancer. The patient had received radium pack treatment to the thyroid area for goiter.

The patient first noticed a change in the shape of his chest about 1939, at which time he began to experience indefinite aches and pains. He had begun to lose weight, having weighed over 200 pounds at one time, became weakened, and noticed that his height was diminishing (maximum height was 71 inches, present height 65 inches). Symptoms of frequency and urgency of urination followed, and about 1940 a suprapubic prostatectomy was performed. He was told that no growth was found.

Two years before admission he tripped on a rug and fractured the left hip and left

humerus. The humerus was impacted and required no immobilization. The femur was treated by insertion of a Smith-Petersen pin. The family was told that the bone was abnormally spongy. Following this he was up and about with the aid of crutches.

About 6 months before admission he developed a diffuse itching of the skin which persisted. Two months before admission he had a painful pruritic eruption of the right side of the back which was diagnosed shingles. The day prior to hospitalization he began to have sharp sticking pains in the left lower quadrant when he moved his body and when he urinated.

of the fingers. The left leg was 1 inch shorter than the right. Movement of the left leg caused pain in the lower abdomen. The back showed a marked thoracic kyphosis with slight scoliosis.

The head was of normal configuration. The eyes were essentially normal except for impaired vision, band-shaped keratitis bilaterally, and right senile entropion. Hearing was impaired. The oropharynx was negative. The patient was edentulous. The lobes of the thyroid gland were enlarged and nodular.

Expansion of the chest was limited considerably. Lung fields were clear. The heart was not enlarged. Sounds were distant.



FIG. 9.—Part of a minute oxyphil cell adenoma (CASE 3). It is well circumscribed and the surrounding chief cells are arranged in cords and appear compressed. (X 150.)

Gastrointestinal tract: Appetite had been finicky for the past 3 months. There were frequent episodes of constipation but no diarrhea. He had vomited after breakfast for the past 10 days. Cardiorespiratory tract: Essentially negative. Genito-urinary tract: Nocturia 3 times nightly. No hematuria and no history of renal colic.

Physical Examination. A poorly nourished bedridden white male who appeared chronically ill and older than his 70 years. There were deformities of the chest (lateral narrowing), left hip, left shoulder, and joints

Blood pressure 130/80. The abdomen was soft and no masses were palpable. There was tenderness in the left lower quadrant. A midline surgical scar was present below the umbilicus. Rectal examination disclosed no masses. The prostate was normal. The genitalia was normal.

The skin was pale, dry, and thin. Scars of herpes zoster were present along the right upper chest wall. Small, shotty lymph nodes were palpated in the neck, axilla, and groins. The reflexes were active and equal. There were no pathological responses.



FIG. 10.—Roentgenogram of left humerus shows osteoporosis and a cystic area. There is evidence of a healed fracture of the surgical neck. (CASE 4.)



FIG. 11.—Roentgenogram of pelvis shows the migrating Smith-Petersen pin extending through the left acetabulum. There is an old unreduced fracture of the neck of the left femur. Osteoporosis and cystic changes are present. (CASE 4.)

Special Examinations and Laboratory Data. Roentgenographic studies (Figs. 10, 11, 12) showed generalized osteoporosis of the long bones and numerous cystic areas. There appeared to be some increase in thickness and density of the bones of the cranial vault. Evidence of a healed fracture of the surgical neck of the left humerus was present. There was an old unreduced fracture of the anatomical neck of the left femur. A migrating Smith-Petersen pin was seen extending through the acetabulum into the pelvis. A barium enema was negative. Electrocardiograms were abnormal, showing atrioventricular block and evidence of myocardial damage. Cystoscopic examination showed a trigonitis and elevation of the trigone on the left due apparently to external pressure by the Smith-Petersen pin.

and 19.5 mg. Seven serum phosphorus determinations ranged between 3.4 and 4.4. Urinary calcium excretion determinations showed increased 24-hour output. The alkaline phosphatase was slightly elevated (4.5 and 6.8 Bodansky Units). The serum proteins were 6.9 mg. with normal albumin-globulin ratio. Bence-Jones protein was negative.

The first impression was that the patient had Paget's disease of bone and it had been proposed to remove the migrating Smith-Petersen pin. However, during the time that effort was being made to improve his general condition and the uremic state it became apparent through further studies of the blood chemistry that the true diagnosis was osteitis fibrosa cystica generalisata (von



FIG. 12.—Roentgenogram of skull shows some increase in thickness and density of the bones of the cranial vault. This roentgenological finding was largely responsible for the early impression that the patient had Paget's disease of the bone. (CASE 4.)

A moderate anemia was present. The initial blood count was: Hemoglobin 10 gm.; RBC, 3,250,000; WBC, 9,200 (neutrophils 92%; lymphocytes 8%). Urinalyses showed traces of albumin with moderate to many WBC, few RBC, and no casts. Specific gravities ranged between 1.003 and 1.012. P.S.P. showed 10% excretion of the dye at the end of the first hour and 10% at the end of the second hour. Sixteen N.P.N. readings ranged between 49 and 200 mg. Six serum calcium determinations ranged between 14

Recklinghausen's disease), secondary to a parathyroid adenoma.

Preoperatively the patient was restless and averse to eating. He complained of dryness of the mouth, itching of the skin, and occasionally vomiting. Cheyne-Stokes respiration was present at times. On June 19, 1946, a weakness of the left arm was noted. He developed a fecal impaction, following which he had diarrheal stools for several days. Although there was apparent improvement in the uremic state, his general condition

did not improve. At the onset he was able to be out of bed in a wheel chair for an hour, but later he could not be encouraged to get up at all. The pulse rate varied between 100 and 120 per minute and there were occasional extra systoles. Urinary output was within the normal amount.

Postoperative Course. On the day of operation the patient was given 20 cc. of 10% calcium gluconate (2 gm.) intravenously and 2 cc. (20 units) of parathyroid extract intramuscularly. On the following day he received with intravenous fluids 40 cc. of 10% calcium gluconate (4 gm.), and 20

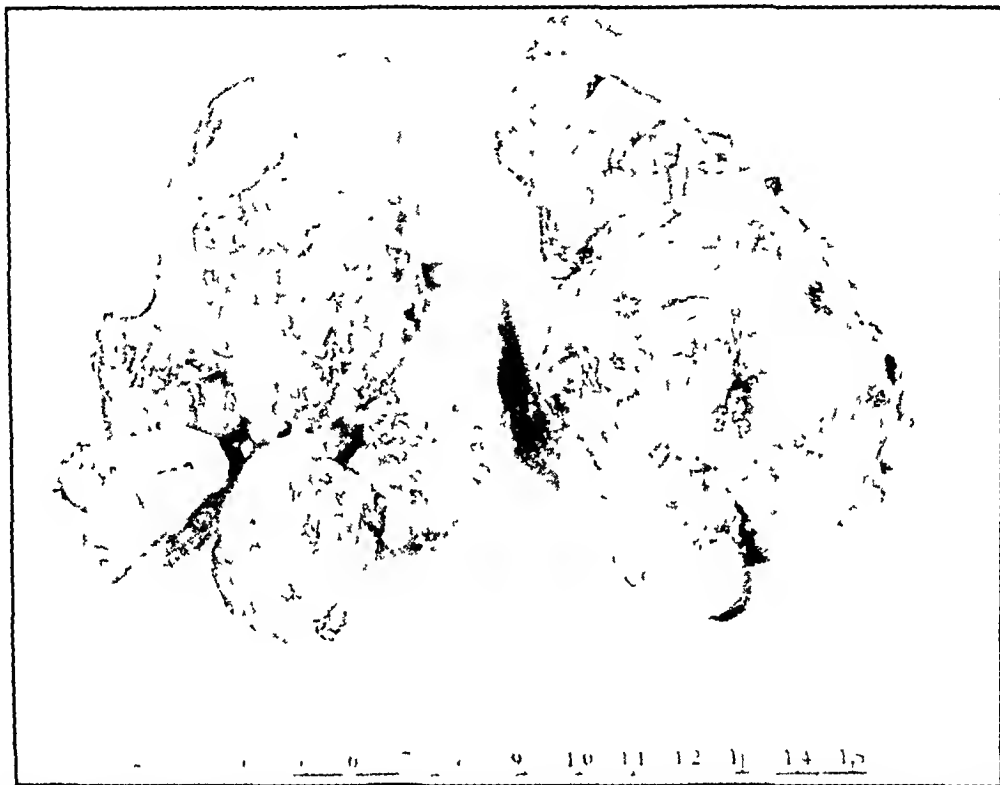


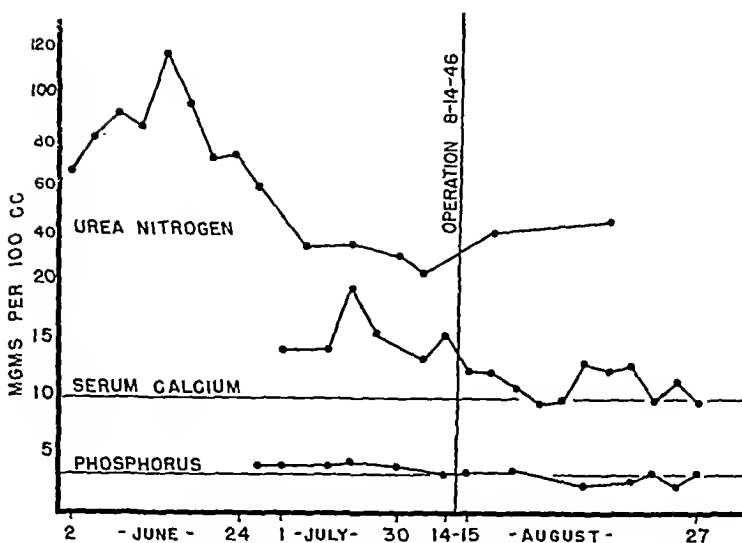
FIG. 13 — Thyroid gland and parathyroid adenoma (surgical specimen). The thyroid is enlarged and nodular. The tumor (sectioned) at the right lower pole of the thyroid weighed 10 gm. and measured $3\frac{1}{2} \times 3\frac{1}{2} \times 2$ cm. The cyst can be seen (CASE 4.)

Operation. On August 14, 1946, under endotracheal general anesthesia, exploration of the neck was done. The thyroid was enlarged and adenomatous with degenerative changes throughout consisting of small cysts and calcified areas. At the lateral border of the right lower pole posteriorly, in the tracheo-esophageal groove, was a grayish-yellow, soft, lobulated tumor which contained a cystic area $\frac{1}{2}$ cm. in diameter, with a partially calcified wall and a calcified nodule $\frac{1}{2}$ cm. in diameter in the center (Fig. 13). The tumor was distinctly paler and softer than the thyroid lobe to which it was attached by connective tissue. It measured $3\frac{1}{2} \times 3\frac{1}{2} \times 2$ cm. and weighed 10 gm. The other parathyroid glands were not seen. The tumor and most of the thyroid gland were removed.

units of parathyroid extract intramuscularly. Dihydratichysterol $\frac{1}{2}$ cc. was given orally that evening. Daily thereafter he was given $\frac{1}{2}$ cc. of dihydratichysterol until August 25, 1946 (eleventh postoperative day), at which time he refused to take some of his oral medications and it was not thought necessary to continue it.

The blood chemistry findings, including urea nitrogen, calcium, and phosphorus, are shown in Figure 14. Postoperatively the serum calcium was seen to fall to normal by the fourth day and then to rise again. The possibility of another parathyroid adenoma was considered.

On the first postoperative day the urinary output measured 850 cc. The patient did not develop an oliguria although he had difficulty in voiding and required catheteriza-



GRAPH SHOWING PRE- AND POSTOPERATIVE BLOOD
CHEMISTRY FINDINGS

FIG. 14.—Preoperative and postoperative chemical findings. Preoperatively, there was improvement in the uremic state. Repeated serum calcium values were elevated. Serum phosphorus values were within normal range, presumably because of the renal damage.

Postoperatively, on the day of surgery and the first day after surgery, he was given calcium gluconate and parathyroid extract. Subsequently he took, orally, $\frac{1}{2}$ cc. of dihydrotachysterol each day until the eleventh postoperative day. The serum calcium is seen to fall to normal by the fourth day and then to rise again. Because of this, the possibility of another parathyroid adenoma was considered. (CASE 4.)



FIG. 15.—Lung Calcium deposits are seen in the alveolar septa; there is much connective tissue reaction. (CASE 4. $\times 300$.)

tion. He remained apathetic and at times was noisy and confused. He had difficulty in raising accumulations of mucus from the throat, and nose and throat examination showed that he had developed paresis of the inferior laryngeal constrictor muscles. Electrocardiograms disclosed an auricular fibrillation. It became difficult for him to swallow food or liquids and at times respirations came slow and labored. Considering his poor condition preoperatively, the postoperative state was not thought alarming until August 29 (fifteenth postoperative day) when he suddenly became dyspneic and expired within a few minutes.

chyma, especially about the cysts. Division between cortex and medulla was indistinct. No calculi were present in the rest of the urinary tract. The urinary bladder and ureters were grossly normal. There was no obstruction to the bladder neck. The prostate was small. The Smith-Petersen pin had migrated a distance into the pelvis 4 cm. from the left acetabulum to the left side of the sacral promontory. It was covered only by peritoneum. The bony skeleton showed a soft round area, $1\frac{1}{2}$ cm. in diameter, in the left parietal bone of the skull. A hard nodular area was observed in one rib. The



FIG. 16.—Kidney. Calcium deposits are present in and about the tubules (nephrocalcinosis) with reactive fibrosis. (CASE 4. $\times 150$.)

Necropsy. The surgical neck wound was well healed. There was a decubitus over the midthoracic vertebrae. Body weight was about 98 pounds. Careful search for parathyroid tissue was made in the neck and in the anterior and posterior mediastinum, taking many specimens for histological study. None was found. Only about $\frac{1}{2}$ gm. of thyroid tissue remained at the right upper pole. There were no significant findings in the heart and lungs. The aorta showed severe arteriosclerosis. The gastrointestinal tract was negative. A calculus 1 cm. in diameter was present in the gallbladder. The kidneys were markedly contracted and had coarsely granular surfaces; each weighed 50 gm. Cut section showed several cysts with thick, partially calcified walls. Gritty, yellow granules were present throughout the paren-

chyma of the left clavicle and lumbar vertebrae showed no gross change.

Significant Histopathological Findings. There were calcium deposits in the alveolar septa of the lungs with fibrous reaction (Fig. 15). Calcium was also present in considerable amounts in the parenchyma of the kidneys (Fig. 16). There was much associated reactionary fibrosis and the glomeruli were badly damaged, many of which were hyalinized and fibrosed. There was mild hyperplasia of the prostate. Some sections of the bone showed proliferation of fibrous tissue with thinning of the trabeculae. Most sections were not unusual, however. There was considerable fibrosis in the spleen. No evidence of calcification was seen in sections from the gastrointestinal tract. The brain disclosed moderate gliosis. The small

vessels were thrombosed and there was some degeneration of the nerve cells, showing pigmentation. There was calcification in the media of the small arteries in sections taken from the neck.

Histological examination of the parathyroid adenoma showed it to be composed largely of chief cells with islands of pale oxyphil cells present here and there. There was considerable dense connective tissue running in bands which had divided the tumor

of staining. The cells were especially distorted in the dense connective tissue and calcified zones. Few mitotic figures were present. There was no evidence of invasive tendency.

Best Carmine stain disclosed fine glycogen granules in the cytoplasm of the chief cells but not in appreciable amount in most areas. Special staining (Sudan IV) showed no fat in the tumor cells.

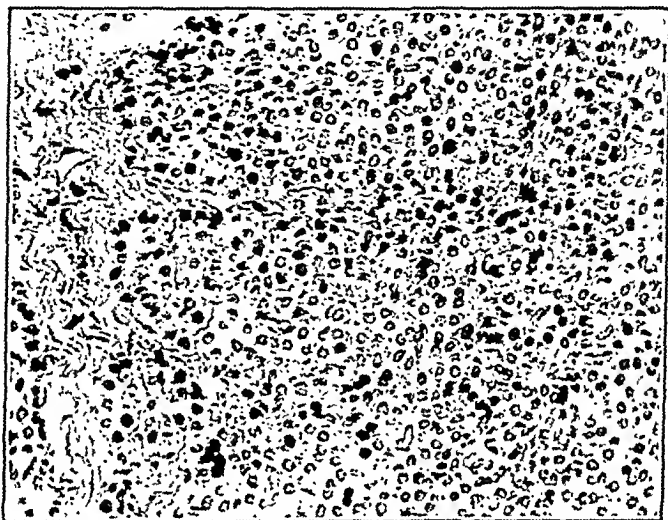


FIG. 17.—The parathyroid adenoma. Section shows the chief cells arranged in a continuous mass. A dense connective tissue septum is seen on one side. (CASE 4. $\times 400$.)

into lobulations. Various cell patterns were present, including areas of many small follicles, arrangement of cells in cords, and arrangement of cells in broad sheets, the latter being most common (Fig. 17). There were calcified areas, one large cyst, a very vascular area, and an area with marked hyaline changes among the cells. In some sections the cells varied considerably in size and shape. In most sections the cytoplasm stained uniformly but there were a few areas in which there was vacuolation. The nuclei also varied in size and shape and in intensity

Summary. A study of the parathyroid gland, based, in part, on 60 postmortem examinations, has been presented. It includes a review of the embryology, anatomy, and histology. Consideration is given to the mechanism of hyperparathyroidism and its clinical manifestations. Certain histopathological features are discussed. A case of osteitis fibrosa cystica generalisata (von Recklinghausen's disease) associated with parathyroid adenoma, including necropsy findings, is reported.

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THE OCCURRENCE OF GASTRIC NEOPLASMS IN YOUTH*

* Aided by a grant from the Earhart Foundation.

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GASTRIC carcinoma in individuals 30 years of age and younger is a rare disease. In 1941 McNeer³ reviewed the world literature on this subject and found 501 cases below the age of 31 and in which the diagnosis was reasonably justified. In addition, he reported 5 cases of his own, collected from a total series of 682 cases of gastric cancer, an incidence of 0.7%. In the earlier literature Welch⁶ reported an incidence of 2.8% of gastric carcinoma in this age group of a total of 2038 cases. More recently, Walters and his co-workers⁴ collected 24 instances of gastric carcinoma between the ages of 24 and 29 from a total of 2772 resected cases. By considering all cases of carcinoma of the stomach, Walters, Gray and Priestley⁵ reported the largest single series of carcinoma in youth. Of a total of 10,890 cases there were 90 below the age of 30 with carcinoma of the stomach. The youngest case in this series was a male aged 18.

Because of the rarity of this condition in youth, there has been a frequent tendency either to overlook this diagnosis when the patient is 30 or younger, or if there is clinical and roentgenologic evidence of a gastric lesion to consider other diagnostic possibilities to be more likely. Benign gastric ulcer, gastric lues or gastric lymphoblastoma is usually considered to be the more probable diagnosis, in view of the patient's age. As McNeer³ pointed out in his review, the roentgenologic evidence of carcinoma is ignored or not considered seriously because of the age of the patient.

As a result of this tendency various forms of therapy are resorted to, often for many months before surgical intervention is undertaken. Because of this delay in treatment the prognosis of gastric carcinoma in youth is often permitted to become worse than for older age groups.

Since the primary obstacle in making the diagnosis of carcinoma of the stomach in youth appears to be the patient's age, an effort was made to discover from the literature what the statistical possibilities are that any gastric lesion occurring below the age of 31 is a carcinoma. There is very little evidence on this subject and one is surprised to find that there has been no parallel evaluation of the incidence of benign gastric ulcer and gastric carcinoma in youth (below the age of 31) in any large series of patients. Comfort and Butsch¹ found that benign gastric ulcer in the third decade of life was 20 times more prevalent than was cancer. However, their figures were based on a small group of resected cases in which the lesion was 4.4 cm. in diameter or less, and, as the authors point out, the figures do not represent the actual total incidence of either of the 2 diseases. Likewise, there has been no parallel study of the incidence of other gastric lesions such as lymphoblastoma, benign gastric tumors and gastric lues with gastric carcinoma in youth in any large series of patients. As a result of our failure to find any such parallel data in the literature on either the incidence of benign gastric ulcer or other gastric lesions,

such as lymphoblastoma and leuc, in comparison with gastric carcinoma in youth, we felt that the usual clinical dictum that a gastric lesion in a patient below the age of 31 is probably benign was not necessarily justified.

In order to study this problem, a survey was made of the total incidence of gastric carcinoma at the University Hospital during a 20-year period (July 1, 1925 to June

30, 1945). During this period there were 453,400 registrations and during the same period 1913 instances of carcinoma of the stomach (an incidence of 0.42%), which means that in this institution 1 out of every 225 patients registering here has a carcinoma of the stomach. In Figure 1 the age and sex distribution for all cases of carcinoma of the stomach are indicated. This general age and sex distribution is in

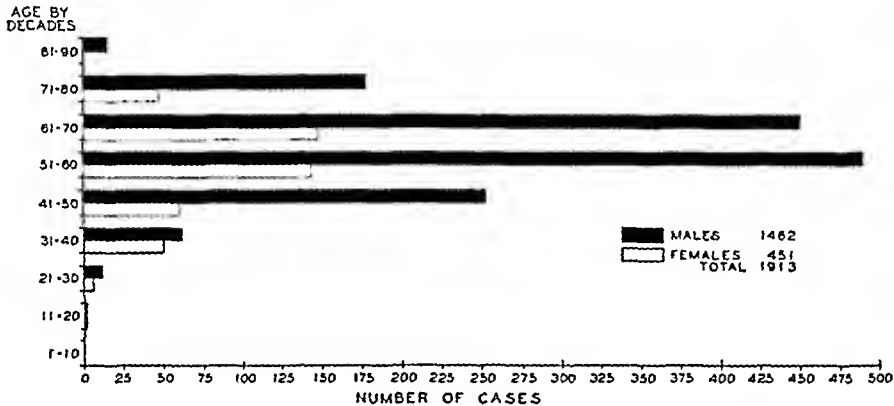


FIG. 1.—Incidence of carcinoma of the stomach during 20 year period by sex and age (July 1, 1925 to June 30, 1945).

close agreement with previously reported surveys.^{2,5} Two points in these data seem to us of considerable interest. First of all, there is an absence of any case of carcinoma of the stomach in any female patient over the age of 80. The second point, and more pertinent to our present study is the occurrence of 20 instances of carcinoma of the stomach in patients below the age of 31. This is an incidence of 1.04% of 1913 gastric carcinomas. This figure is in general agreement with the 0.7% incidence reported by McNeer³ and the incidence of 0.8% of Walters *et al.*⁵

Since our primary interest was in the younger age group a detailed study was made of these 20 instances of carcinoma of the stomach. Table 1 shows the age and sex distribution for this group. Our youngest case was 16 years old, with 13 cases occurring at 25 years of age or older. There were 13 males to 7 females, or roughly 2 to 1. Figure 2 indicates the fre-

TABLE 1.—AGE AND SEX DISTRIBUTION OF 20 CASES OF CARCINOMA OF THE STOMACH IN YOUTH

Age	Number	
	M	F
16	1	
18	1
21	1
22	2	
23	1	
24	1
25	1
26	2	
27	2	
28	2
29	2	
30	3	1
Total	13	7

quency of symptoms in all 20 cases. Of particular significance was the fact that gastric distress or pain was a prominent and important symptom in 17 cases. Although this epigastric discomfort was usually somewhat different from that occurring in benign gastric ulcer, nevertheless, its frequent occurrence as a promi-

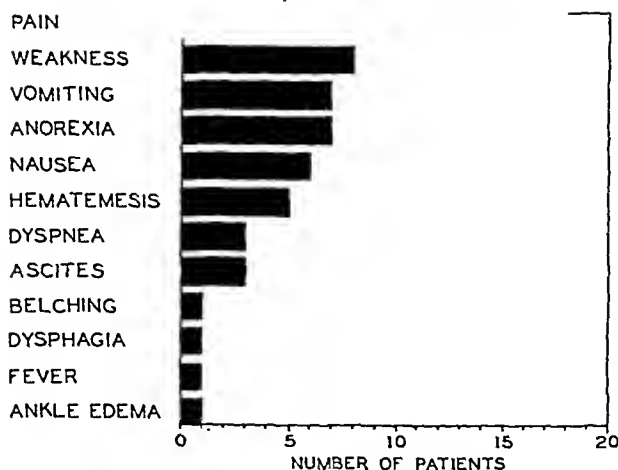


Fig. 2.—Symptomatology in 20 cases of carcinoma of the stomach below age of 31.

nent symptom discouraged the clinical suspicion or diagnosis of neoplasm. The frequency of hematemesis (5 instances) had the same clinical significance, particularly in view of the fact that in 3 instances

hematemesis was the initial symptom. Other pertinent data in the entire series are graphically represented in Figure 3. These data are those obtained at the time of the original examination at the Uni-

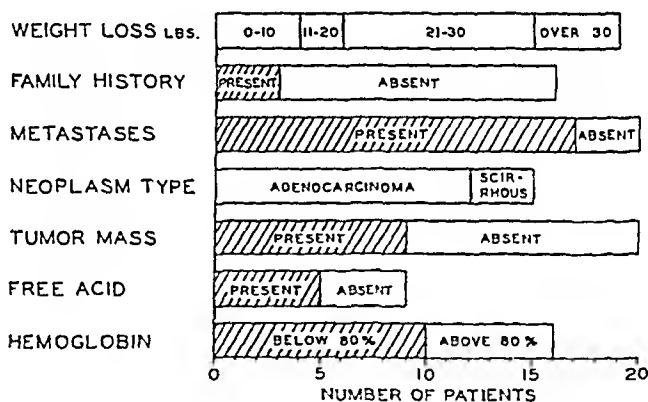


Fig. 3.—Pertinent data on 20 patients 30 years old and below with carcinoma of the stomach.

versity Hospital and generally reveals the fact that at this time the disease was far-advanced. In 9 instances (45%) there was a palpable tumor mass, and in 17 cases (85%) metastases were demonstrable either clinically or at the time of operation. In fact, metastases were so marked that definitive surgical therapy was considered feasible and carried out in only 3 cases. Fifteen other cases were subjected to an exploratory laparotomy and metastases confirmed. In 2 instances metastases were demonstrable by lymph node biopsy. In 5 of the 9 cases subjected to gastric analysis

free acid was present. Weight loss was significant in 16 instances and definite anemia was present in 10 cases. Of great interest was the occurrence of a family history of gastric neoplasm in only 3 patients (15%). This figure does not differ greatly from the incidence of 20% reported by Walters.⁵

The delay in diagnosis and course of the disease after the diagnosis was established is indicated in Figure 4. Of great significance is the fact that in 5 cases (25%) the diagnosis was not established until 19 to

24 months after the onset of symptoms. Actually, in all 5 cases included in the 19 to 24 month period, the diagnosis was established at the upper limit of this period, 24 months after onset of symptoms.

The average time for diagnosis after onset of symptoms for all cases was 11.5 months. The time of death was known only in 14 cases and the average duration of life after the onset of the initial symptoms in this

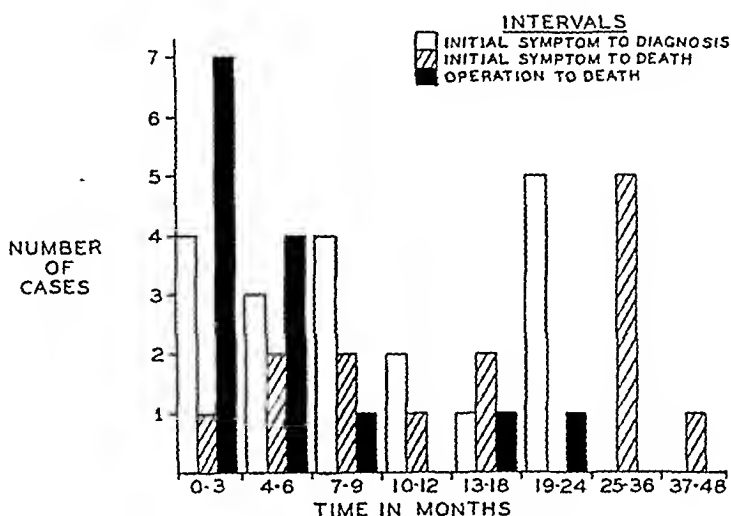


FIG. 4.—Diagnostic and prognostic intervals in 20 cases of carcinoma of the stomach in youth.

group was 17.4 months. In 1 instance death occurred within 3 months (Figure 4). The duration (average 5.3 months) of life after operation is not a criterion of the efficacy of surgical treatment in our series, since as previously indicated, metastases were present in 85 % at the time the patient was first examined. In the 3 instances where definitive surgery was considered feasible and carried out, the postoperative duration of life was 5, 15, and 23 months respectively.

The delay in diagnosis in most cases was associated with two facts: (1) The failure of the patient to consult a physician early after the onset of symptoms and (2) the fact that because of the patient's age, there was a tendency on the part of the physician not to diagnose neoplasm in spite of suggestive and even definite clinical and roentgenologic findings. Benign gastric ulcer was nearly uniformly considered a more likely diagnosis. In 8 of our 20 cases it

TABLE 2.—DATA OF PATIENTS WITH INITIAL DIAGNOSIS OF PEPTIC ULCER

Case No.	Clinical story	Initial Roentgen ray findings	Intervals from operation to death
1	Recurrent gastric distress for 10 years. Treated intermittently for ulcer.	Negative	1 month
2	Ulcer-like symptoms for 5 years. Diagnosis of peptic ulcer.	Diagnostic of neoplasm	2 weeks
3	Epigastric distress for 2 years. Treated for ulcer.	Negative	5 months
4	Diagnosis of gastric ulcer. Treated for 33 months.	Gastric ulcer, regression, then recurrence	9 months
5	Diagnosis of aerophagia 6 years prior to discovery of neoplasm. Ulcer diagnosed 4 years later. Relief by diet.	Diagnostic of neoplasm	23 months
6	Epigastric distress for 2 years. Treated for peptic ulcer.	Diagnostic of neoplasm	2 months
7	Abdominal discomfort and cramping for 5 years. Treated for ulcer	Gastric ulcer	Exact time of death unknown
8	Five year history of ulcer type of distress.	Diagnostic of neoplasm	5 months

was possible to demonstrate that the patient had consulted a physician soon after the onset of symptoms, but a diagnosis of gastric ulcer was made and the patient treated medically. Data on these 8 cases is summarized in Table 2. The initial Roentgen ray findings at the University Hospital are indicated and it is of

interest that 2 were negative, 2 were considered diagnostic of benign gastric ulcers and 4 were diagnostic of gastric neoplasm. Case 4 is of particular interest in that the original diagnosis was benign gastric ulcer March 8, 1938 (Figure 5). Partial healing seemed apparent on Roentgen ray within 3 weeks. This partial healing was accepted

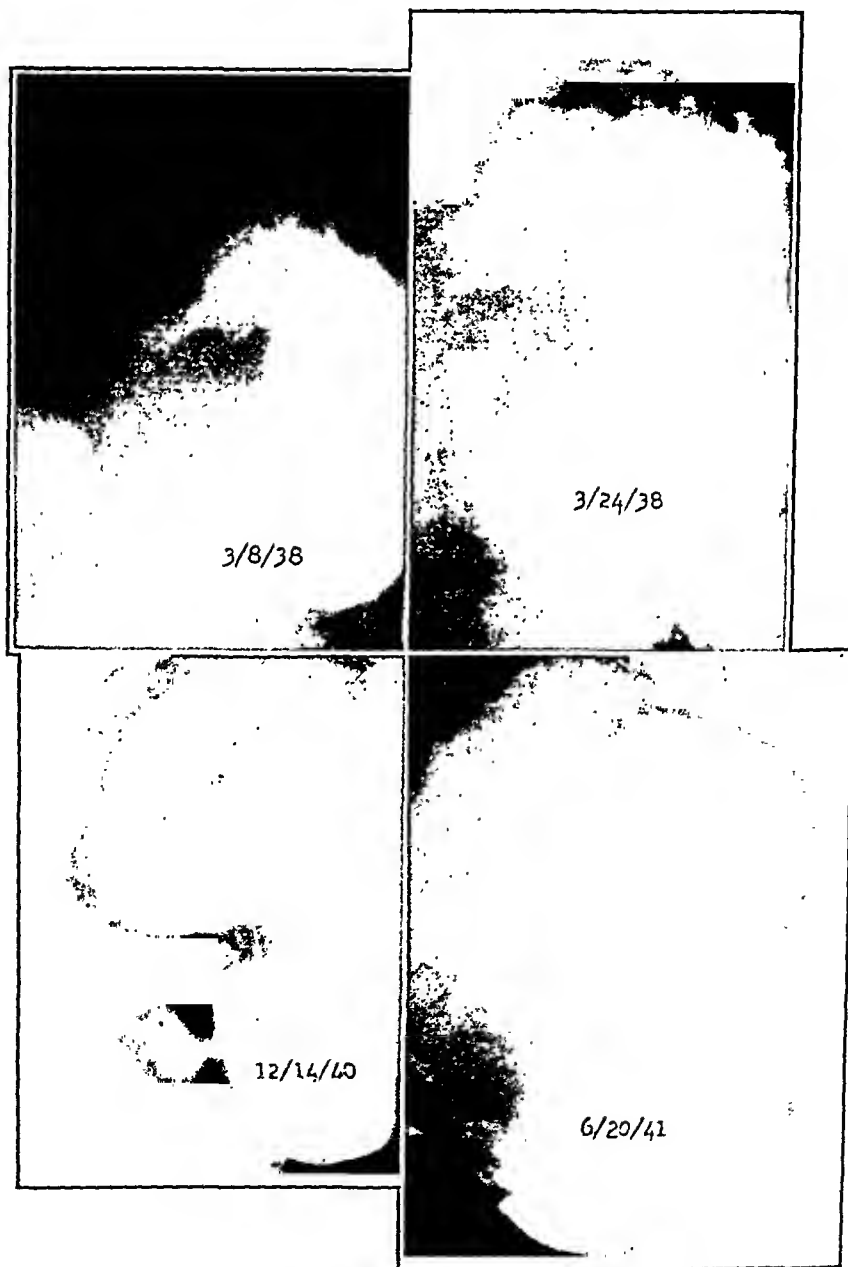


FIG. 5. —Case 4: Progress of gastric lesion originally regarded as benign (March 8, 1938). Neoplasm suggested by roentgenologist December 14, 1940 and metastases (supraclavicular lymph node) demonstrated June 20, 1941.

as definite evidence of benignity of the lesion and there was no further follow-up until recurrence of symptoms in December, 1940. At this time (Dec. 12, 1940) the roentgenologist first suggested the diagnosis of gastric neoplasm. In view of the patient's age the clinician ignored this suggestion and continued medical therapy until June 20, 1941, when definite metastasis was present. Death occurred 9 months later. It is not pertinent to this report to discuss whether or not this was an instance of malignant degeneration of a benign ulcer or whether this ulcer was throughout its course a malignant ulcer. However, two points are worthy of emphasis. First, because of the false security

that the patient's age gave the clinician, the patient was not followed as closely as indicated. Secondly, because of the patient's age the occurrence of a gastric ulcer which did not remain healed did not appear to be an indication for surgical intervention as would have been the case in an older patient.

In view of this general tendency to consider that gastric lesions in youth are more likely to be benign than malignant, a survey was made of all gastric lesions that had occurred in individuals below the age of 31 during the same 20-year-period. Results are shown in Figure 6. There was a total of 73 gastric lesions in this age group. Fifty of these were benign ulcers, 20 were

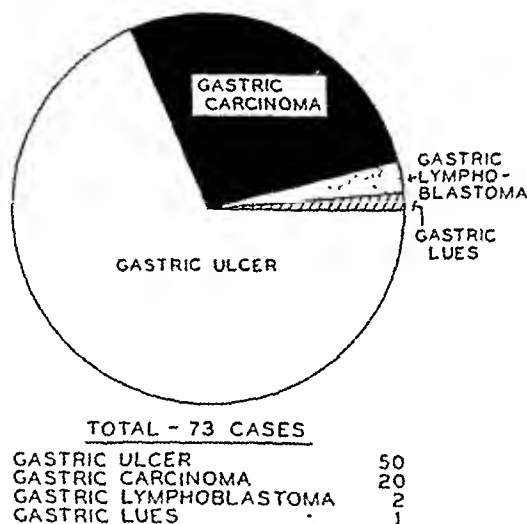


FIG. 6.—Incidence of all gastric lesions in patients under 31 years of age during 20 year period.

carcinomas, 2 were lymphoblastomas and 1 was gastric lues. This indicates that in this age group, although gastric lesions are rare, when one does occur there is approximately a 30% chance that it is a carcinoma. If one includes the 2 cases of primary gastric lymphoblastoma, the chances that a gastric lesion occurring below the age of 31 is neoplastic are even more impressive.

Summary and Conclusions. 1. A survey of the occurrence of carcinoma of the stomach during a 20 year period (July 1, 1925, to June 30, 1945), at the University Hospital revealed that there were 1913 carcinomas out of a total of 453,400 registrations. This is an incidence of 0.42%.

2. Of the 1913 carcinomas during this same period, 20 (1+%) occurred in patients below the age of 31. Of these 20 cases, 17 had metastases when first examined, and the diagnosis of carcinoma was usually delayed because benign gastric ulcer was generally considered the more likely diagnosis in view of the patient's age.

3. During the same 20 year period 53 other gastric lesions (50 benign gastric ulcers, 2 gastric lymphoblastomas, 1 gastric lues) occurred in the same age group.

4. These figures demonstrate that all gastric lesions are rare in patients below the age of 31, but once a gastric lesion does occur the probability that it is neoplastic is at least 30%.

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PLASMOCYTOMA (MULTIPLE MYELOMAS, KAHLER'S DISEASE), AND ITS ATTENDANT DISTURBANCES IN THE PROTEIN METABOLISM

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I. *All multiple myelomas are plasmocytomas.* In the Netherlands Medical Journals articles dealing with the above-mentioned subjects have repeatedly appeared during the last few years. None of the authors of these articles, however, has ventured definitely to side with those modern views which are beginning to gain ground, and which enable us to survey this field of study, formerly of a most confused nature, from one central point of view.

We are now in possession of sufficient facts and arguments to justify us in provisionally adopting the system to be described herein, considering afterwards those cases which do not fit in with this system. No such exceptional case, however, has so far come to our notice, although Apitz sharply defined the modern conception as early as 1939 and 1940.^{1,2,3}

We have seen new cases of plasmocytomas within a brief period of time, and one of us, together with Van Dam⁶ described a case of paramyloidosis (primary amyloidosis) some years ago that may also be classed with the same group. The clinical data of these cases are given below in the form of tables. It may be gathered from these data that, in these patients, the classical phenomena of multiple myelomas—pains, curvatures, spontaneous fractures, holes in the skiagrams of the bones—were often not predominant.

Many different kinds of multiple myelomas used to be recognized. It was thought that any cell occurring in the bone marrow might give rise to a given kind of myeloma. This conception was mainly based upon an erroneous interpretation of histologic preparation, which did not allow of more refined cellular diagnosis. The difficulty experienced formerly is shown clearly in

Reisberman's case:²¹ in the sternal puncture he found 586 plasma cells per 1000; but in the histological sections of the spinal marrow no plasma cells could be discovered.

Ever since sternal puncture was introduced into diagnostics, and since, therefore, hematologic differentiation of the various forms of cells has become possible, no further communications concerning all these different forms have appeared, and only one form of myeloma has been described, *i. e.*, the *plasmocytoma*.

As long ago as 1936, Patek and Castle²⁰ replaced the name myeloma by that of plasmocytoma. They pointed out that, between the different forms of plasma cell tumors, there exists a relation similar to that between the different forms of lymphocytic growths (lymphocytoma, lymphosarcomatosis, lymphatic leukemia).

Rohr²⁴ says that the typical myeloma is built up from plasma cellular reticulum cells, by which he means that these plasma cells are originated from reticulum cells, which point has no further bearing on our problem. The reticulum cell as understood by hematologists is something different from the conception which the pathologist-anatomist has of it.

Apitz drew up an easily surveyable schematic representation, which is here reproduced (Fig. 1):

1. The locally increased plasma cell exists only hypothetically.

2. It is not certain whether or not the solitary plasmocytoma can occur without diffuse increased plasma cell formation. In any case sternal puncture should be performed *before proceeding to operation*.

3. Diffuse plasmocytosis was, and still is, generally misconceived, and called

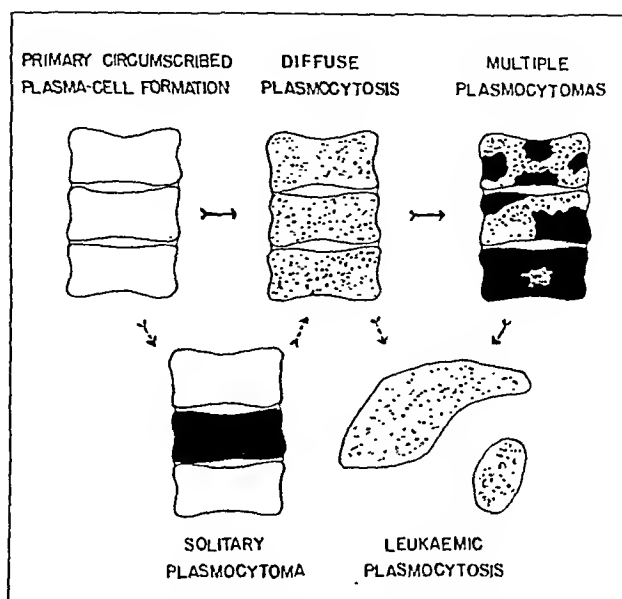


FIG. 1.—Illustrating the interrelation between the different clinical types of plasmacytosis.

either osteoporosis or senile osteoporosis.

With the aid of sternal puncture these diffuse plasmacytoses may be recognized. Pathologic anatomists can safeguard themselves from drawing erroneous conclusions by making slide preparations from patients with osteoporosis, thus enabling the hematologic diagnosis to be made. The results of such an examination in one of our cases are described later on. Naegeli points out that slide preparations should be made as soon as possible after death.

In diffuse plasmacytosis no more than 1 to 3% plasma cells are generally found in the peripheral blood; they may be compared to aleukemic leukemias. They may also turn leukemic quite suddenly, although no more than 50,000 plasma cells per c.mm. are usually found, whereas, in common leukemia, much higher figures are reached. This is a variety of leukemia with "stay-at-home" cells. In these leukemias, too, one frequently finds circumscribed tumors in the bones.⁴ It is no longer of great significance whether in these cases we speak of plasma cell leukemia or of plasmacytoma.

4. Multiple plasmacytomas are a long known form of multiple myelomas. They may be clearly seen on Roentgen photos,

resembling moth-holes. It is important for the diagnosis that, between the tumors, a diffuse plasma cell formation is said to be found in every case; it is not, therefore, absolutely necessary to strike the tumor itself when performing sternal puncture. When considerable plasma cell formation is found, especially with atypical and polynuclear plasma cells, one may safely diagnose plasmacytoma, remembering that, in such conditions as kala azar, lymphogranuloma inguinale and agranulocytosis increased plasma cell formation also occurs. It is not necessary, therefore—as Mansens would have one do^{15,11}—to cut up a corpse millimeter by millimeter so as to exclude the possibility of a single plasmacytoma.

An hour and a half after the decease of our patient I, we made slide preparations from freshly-cut pieces of tissue from the bone marrow, the liver, the spleen, and the lungs. In all these stained preparations we were able to find plasma cells in very large numbers. § Mills and Pritchard did the same with a piece of bone obtained by trepanning.¹⁹ ¶ In the slides from the bone marrow and the spleen we hardly found any other cells. They have a round nucleus with a distinct nucleolus. The nucleus lies

eccentrically, in a blue, slightly granulated protoplasm, with a lighter-colored area around the nucleus. In fairly large parts we found only naked nuclei. The protoplasm appeared to have run for the greater part, as the intermediary substance showed the same color as the protoplasm of the plasma cells.

This technique of staining cells shortly after death enables the pathologist-anatomist to come to a far more exact diagnosis than the customary pathologic-anatomic section preparations.

II. *Protein metabolism disturbances in cases of plasmocytoma.* Bence-Jones protein is to be distinguished as is well known, from the common variety of albumin in cases of albuminuria in that it precipitates at a temperature of 40° to 60° C., it dissolves completely when boiled, and on cooling below 60° reappears. When, in addition to Bence-Jones protein, there is also albumin of another kind present in the urine, the latter may be precipitated by boiling after adding a few drops of acetic acid. The boiling urine should be filtered immediately. When the clear filtrate cools down to 65° C., it becomes cloudy through the reappearance of Bence-Jones protein, which cloudiness disappears on re-boiling, etc.

Snapper succeeded in demonstrating the presence of Bence-Jones protein very well indeed by adding one-tenth of the volume 20% sulphosalicylic acid before boiling. Schalm,²⁵ however, points out that, by this method, the reaction turns out positive in a large number of cases of albuminuria; it is probable, therefore, that the Bence-Jones albumin is formed during boiling with sulphosalicylic acid, so that in this way the reaction loses its diagnostic value.

The Bence-Jones protein sooner or later begins to precipitate in the renal tubules; it forms cylinders which may block up the nephrons and tend to set up intrarenal hydronephrosis. When many nephrons have been eliminated in this way the patient dies from uremia.

In from 65 to 80% of sufferers from plasmocytoma Bence-Jones protein is

found in the urine. Apitz is of the opinion that it is formed by the plasmocytoma cells. Then it does not occur unless the patient is suffering from a plasmocytoma! The general opinion used to be very different; Bence-Jones albumin has been described in cases of patients with all possible kinds of bone diseases, fractures, shot wounds, in leukemias, nephroses, etc. We are probably justified now in assuming that, in all cases, one of the forms (generally the diffuse form) of plasmocytoma has been either disregarded or misunderstood. None of the descriptions previously given of such cases can stand Apitz's criticism, and no fresh cases have been described in later years.

The work done by Meyler^{17,18} is not referred to by Apitz; yet it should not be passed over without comment. Meyler was able to demonstrate the presence of Bence-Jones protein in extracts of normal bone marrow, of pus from empyemas, and in extracts from the cells of a lymphatic leukemia. It is open to question, however, whether the Bence-Jones protein, in these cases, was not created by denaturation from normal protein.

Ellinger (1889), whose method was followed by Meyler, was already of the opinion that, after extraction with alcohol for 14 hours, all proteins except the Bence-Jones protein had been denatured. Meyler himself, for that matter, is fairly critical on this point; he condemns boiling with sulphosalicylic acid, because, in that way, Bence-Jones protein can be made out of all animal proteins.

Even though Bence-Jones protein has been shown to be present in normal marrow the possibility still exists that it is extracted from the plasma cells occurring in the marrow, which appears to be confirmed by the fact that it is present in exceedingly small quantities only. Meyler is of the opinion that Bence-Jones protein can be extracted from lymphocytes; in this case, however, it is incomprehensible that he did not succeed in demonstrating its presence in the spleen. If he succeeds in doing so only in the lymphatic leukemia

cells, then the possibility of any confusion with plasma cell leukemia—which is sometimes hard to identify—must be excluded. As far as we are aware, his followers, at any rate Van Melle and Cornelis,¹⁵ have not succeeded in demonstrating the presence of Bence-Jones albumin in cases of leukemia. The fact that Meyler found Bence-Jones protein in a patient whose knee had been smashed is no evidence either way. A sufferer from plasmocytoma, too, may get a smashed knee, and even more easily than anybody else! At this time Meyler's investigations have largely lost their weight as arguments against the plasma-cell theory.

Paramyloid. Primary amyloid is not similar in distribution to ordinary secondary amyloid, *i. e.*, in patients suffering from chronic suppuration conditions or tuberculosis. It does not occur in the parenchymatous organs (liver, spleen, kidneys), but by preference in the walls of the blood vessels, unless it accumulates arbitrarily in some organ such as the heart, the stomach, the trachea or the lung. Further, paramyloid shows some differences in coloring from secondary amyloid. Apitz takes the view that paramyloid is connected with the presence of one of the forms of plasmocytoma. It is also found deposited in the plasmocytoma tissue. Patients suffering from paramyloidosis often have Bence-Jones protein in their urine. Cylinders of both Bence-Jones protein and paramyloid are cleared away by foreign body giant cells.

With paramyloid the story is like that with Bence-Jones protein. As the occurrence of diffuse plasmocytomas failed to have the attention of investigators, they were ignored; no microscopic examination of the vertebrae was made, and, moreover, microscopic examination of sections was inadequate, so that one contented oneself with the diagnosis "osteoporosis," or "bone marrow rich in cells." In 1940, Van Dam and Kolff described a case of primary amyloidosis with marked osteoporosis of the vertebral column. Apitz's publication suggested to us that we were

dealing with a diffuse plasmocytoma, but as unfortunately, the preparations were no longer available, the investigation could not be continued.

Mansens lent good support to the plasmocytoma theory by demonstrating the presence of large numbers of plasma-cells in sufferers from secondary amyloid, either in the diseased organs or in the bone marrow. In Roegholt²³ and Straub's case, however—that of a woman suffering from primary amyloidosis of the tongue—Mansens was unable to find plasmocytoma. In the description of the sternal puncture we read: "double the number of plasma cells and reticulum cells, among which were many large cells with large nuclei, as well as cells with 2 or 3 nuclei." On seeing the preparation one hesitates to make the diagnosis of plasmocytoma; in any event, if this diagnosis is even considered, this case is not of any importance in undermining Apitz's hypothesis.

According to Letterer,^{10,11} amyloid precipitates in the body when there exists a disproportion between a large quantity of a certain antigen, broken-down body protein ("eingeschmolzenes Korpereigenes Eiweiss"), and too small a quantity of antibodies. Only Letterer's view, that this antigen is probably created by leukocytes, should be revised; it must be the pathologic protein products of the plasma cells which serve as antigen.

Hyperproteinemia. A very high globulin content of the blood is found in many patients with plasmocytomas. It is probable that in such cases we are not dealing with any raised globulin content, but an accumulation of pathologic globulin (paraprotein) in the blood (Bondsdröff).

Intracellular accumulation of protein. In the plasmocytoma cells and in the cells of the convoluted tubules the presence of accumulations of protein or crystals may sometimes be demonstrated. As regards colorability, these protein precipitates evince a strong resemblance to Bence-Jones protein and to paramyloid. They strongly indicate the probability that this protein is formed in the plasmocytoma

cells. Very good pictures are given by Apitz and Brass.⁴ The latter's supposition, that these albuminoid formations are actually body proteins resorbed into the plasmocytoma cells, is both incomprehensible and insufficiently founded.

Apitz points to the many properties which the above-mentioned proteins have in common, and proposes to call them "paraproteins."

The paraproteins constitute a group of closely kindred pathologic protein occurring in plasmocytoma; they readily precipitate, are crystallized fairly readily, and may all be colored with congo-red. The *paraproteinoses*, therefore, are a group of diseases of the protein metabolism occurring exclusively in cases of plasmocytoma;

Apitz speaks of "*paraproteinuria*" (Benee-Jones proteinuria); "*paramyloidosis*;" "*paraproteinemia*," and *intracellular accumulations of "paraprotein."* One might wonder if any conclusions could be drawn, with respect to the origin of normal serum protein from the pathologic protein formation described above. In normal plasma cells, too, enclosures and crystals of protein are to be found. In cases of trachoma, indeed, paramyloid might be formed locally by inflammatory plasma cells; we already have pointed to Mansen's investigations. Normal serum protein may perhaps be formed by normal plasma cells. The pathologic plasma cells of the plasmocytoma are the formers of paraprotein. Those cells which morphologically differ

TABLE 1 CLINICAL AND PATHOLOGIC DATA OF 4 CASES OF PLASMOCYTOMA

	Name, Sex and Age			
	Van den B. M., 50 yrs.	Post M., 67 yrs.	V. O. M., 53 yrs.	V. D. V. M., 58 yrs.
Anamnesis and course of disease	12 recurring pneumonias and slight bleeding from nose and gums; no bone symptoms	Abdominal pain with constipation; 6 wks. backache	Anemia; backache	For 1½ yrs. severe backache, gradually increasing in severity; emaciated; vomiting since 5 wks. ago
Objective findings	Pneumonia; no further abnormality	Slight kyphosis; pressure on vertebral column painful	Anemia only	Vertebra and other bones extremely painful on pressure; amyloidosis of smaller arteries, especially in head
Hemoglobin, etc.	Hb., 33%; Cl, 1; lcts., 3000 to 6000; plasma cells, 1%; lymphocytes, 51%; thrombocytes, 24,000	Hb., 70%; lcts., 7300; plasma cells, 0%; lymphocytes, 18%	Hb., 23%; lcts., 5200; thrombocytes, 63,500	Hb., 60%; Cl, 1; lcts., 9200; plasma cells, 0%; lymphocytes, 22%
Bone marrow function . . .	Many pathologic plasma cells	Many pathologic plasma cells	Many pathologic plasma cells	?Marrow rich in cells on autopsy
Erythrocyte sedimentation rate and globulin content . . .	Sed. rate, 150 to 165; globulin, 12%	Sed. rate, 98 to 133; globulin, 8.5%	Sed. rate, 63 to 135; globulin, 4.36%	Sed. rate, 73; globulin 2.1%
Benee-Jones albumin in urine .	++	Alternately + and -	Negative	Probably positive
Other urine abnormalities . .	Alb., 3.5%; erythrocytes	Sporadic erythrocytes and leukocytes	Albumin	Albumin, 5%
Roentgen, osseous system . .	Diffuse osteoporosis of vertebral column and round holes in tubular bones and pelvis	Only diffuse osteoporosis of entire vertebral column	Osteoporosis of vertebral column and pelvis	Osteoporosis of vertebral column and pelvis with fish vertebra and infractions
Cause of death	Uremia	Pneumonia	Died at home 6 mos. after admission	Cachexia
Miscellaneous	Auto-agglutination of erythrocytes in Hayem's fluid; at autopsy: plasma cells in internal organs	Spinal fluid: total albumin 64 mg. % (norm. 15 to 24); out of this globulin, 45 cells ±; Pandey slightly +	Paramyloidosis of artery walls and stomach wall

only little from normal plasma cells (*e. g.*, the cells of plasma cell leukemia) would not tend to give rise so frequently to the occurrence of paraproteinoses (Bence-Jones proteins, etc.). It will be interesting in the future to see whether a given morphologic type of plasma cell induces a given type of paraproteinosis.

Summary. A new concept of plasmacytosis has evolved during recent years,

integrating the various clinical forms of this disease. Whether there is focal, diffuse, or leukemic plasmocytosis, sternal puncture will reveal a general increase in plasma cells and is usually diagnostic. Illustrative cases are reported. The production of Bence-Jones proteinuria, hyperglobulinemia, and primary amyloidosis are discussed in the light of present knowledge.

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ADENINE: ITS FAILURE TO STIMULATE HEMOPOIESIS OR TO PRODUCE PELLAGRA IN A CASE OF PERNICIOUS ANEMIA*

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FOR many years we have been studying various synthetic substances and natural products to determine whether or not they induce blood regeneration in various types of anemia. During the course of our observations we have noted that a number of chemical substances stimulated hemopoiesis in persons with Addisonian pernicious anemia, nutritional macrocytic anemia and the macrocytic anemia of sprue. One of these, thymine (5-methyl uracil), is a pyrimidine base and is a constituent of thymonucleic acid.⁴ After finding thymine effective, we turned our attention to adenine, which also occurs in thymonucleic acid as the base of a nucleotide. It is a purine base, 6-amino purine, as seen in the chemical formula shown in Figure 1.

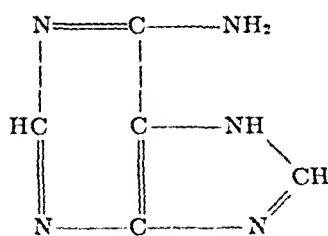


FIG. 1.—Adenine.

Adenine is widely distributed in plant and animal tissues. As a component of thymonucleic acid, it enters into the structure of the nuclei of all animal cells.² It is otherwise present in the body in the free state and as nucleotides which, to some extent, are constituents of enzymes and co-enzymes. Two of them, co-enzymes I and II, are pyridine nucleotides which apparently are formed by living cells from a combination of nicotinamide,

ribose, adenylic acid and phosphoric acid.⁵ The concentration of these co-enzymes in the blood and striated muscles decreases in the pellagrin, and treatment with nicotinamide restores it to normal levels.¹ Spies and his associates also have shown that the administration of co-enzyme I relieves pellagra.³

Recently Raska reported that black-tongue in dogs developed within 7 to 21 days following the administration of from 200 to 500 mg. of adenine daily.³ He believes that this occurred as a result of adenine combining with constituents of the vitamins or their precursors, thus preventing their utilization in the animal. He refers specifically to the possibility of an interference with the formation and activation of alloxin adenine dinucleotides, of the phosphopyridine dinucleotides (co-enzymes I and II) and of the nucleoproteins.

In view of these findings it seemed worthwhile to report our observations on the effect of the oral administration of adenine to human beings. After administering from 5 to 50 mg. each day for from 4 to 10 days to each of several persons with macrocytic anemia in relapse and observing neither toxic manifestations nor blood regeneration, we administered it in larger doses to a patient with Addisonian pernicious anemia in relapse whose case history follows:

CASE 1. The patient, J. D., a 67 year old, married, colored bricklayer, was admitted to the hospital on July 26, 1946 because of symptoms related to pernicious anemia in

relapse. He had been hospitalized on 3 previous occasions, once for an inguinal herniorrhaphy in 1945, and twice (September, 1944 and September, 1945) for the treatment of anemia. At the time of his first admission, he complained of progressive weakness, dyspnea on exertion, slight soreness of the tongue, vague abdominal distress and loss of weight which had begun 9 months previously. He had achlorhydria and achylia after histamine stimulation, and a macrocytic anemia with maturation arrest of the bone marrow cells at the megaloblast early-erythroblast level which responded well to refined liver extract.

When he stopped maintenance therapy, his anemia relapsed and he was readmitted to the hospital for treatment in September, 1945. At that time synthetic folic acid in doses of 50 mg. twice a day was effective in producing blood regeneration and normal blood values. Freedom from symptoms continued until he again stopped maintenance therapy in April, 1946. From that time until his admission to the hospital in July, 1946, there was a recurrence of the following symptoms: general weakness, dyspnea on exertion, slight soreness of the tongue, anorexia and paresthesia of the lower extremities. On admission he appeared rather weak but he was alert mentally and was in no apparent distress while at rest. The conjunctivæ and buccal mucosa were pale; the sclera was cloudy but not icteric; the optic fundi were normal; there was slight redness at the tip of the tongue and the papillæ generally appeared hypotrophic; a systolic murmur was audible over the apex of the heart and blood pressure was 150/80 mm. Hg.; radial arteries were moderately firm; and the lungs were clear and the abdomen negative. The knee and ankle jerks were hypoaffective and vibratory sensation was impaired at the knees and ankles.

The initial blood counts were: RBC 1.86 million, WBC 4350, Hg. 7.0 gm. (45%), Reticulocytes 0.6%, PCV 22%, MCV 118. Blood NPN 23; Kahn negative; icteric index 10; glucose tolerance test normal curve; stool negative; gastro-intestinal series negative; gastric analysis—achlorhydria after histamine stimulation. Urinalysis showed specific gravity 1.020, acid reaction, albumin and sugar negative and microscopic examination negative.

Three days after admission to the hospital on July 29, 1946, 2½ gm. of adenine hydrochloride* twice a day orally was started. Three days later he complained of anorexia and slight nausea, and 5 days later of slight dizziness and a bad taste in his mouth. Meanwhile there were no significant changes noted physically, and he spent considerable time up and about the ward. During the night of the 6th day of adenine therapy, the patient in the next bed reported that this patient (J. D.) had a very restless night, "talked out of his head," vomited, passed a stool in the bath tub and complained that he had trouble thinking and talking. The following morning he appeared very apprehensive and restless and was unable to talk clearly but he seemed fully conscious and attempted to coöperate. The physical findings were as follows:

His eyes at times deviated involuntarily but the pupillary reaction and fundi were normal. The tongue was pink at the tip and edges but did not deviate when protruded and was not tremulous. The lungs were clear. The heart rate was 112, the rhythm normal and the blood pressure 170/110. Neurological examination showed mild rhythmic muscle group contractions involving chiefly those of the forearms and those of mastication; muscle tone generally seemed somewhat increased; however, when an extremity was placed at full rest, considerable relaxation could be obtained; the knee jerks and ankle jerks were slightly more active than on admission but were still normal. No abnormal reflexes were obtained. (The adenine was discontinued—the total dose given was 32.5 gm.) A urine specimen at this time showed: pH 7.5; specific gravity 1.010; albumin trace; sugar negative; no RBC or WBC; sediment thick with amorphous material. The blood NPN had risen from 23 mg. per 100 cc. before adenine was started to 135 mg. per 100 cc.

During the next 24 hours he became worse. Although conscious, he was unable to speak; moderately severe clonic convulsive seizures involving chiefly the upper extremities, cervical, shoulder girdle and abdominal muscles required sodium luminal therapy; the reflexes remained physiologic; and the blood pressure continued elevated. There were no physical signs of increased intracranial pressure and no meningeal signs. There were at no time

* Adenine hydrochloride was furnished by Dr. Earl D. Stewart of Schwarz Laboratories, Inc.

any signs of hemorrhage or ulceration of the eyes, buccal mucosa, skin, gastro-intestinal or genito-urinary tracts; there were no signs of dermatitis and no clinical evidence of acidosis. The mild degree of glossitis present on admission was not altered. Urine specimens contained from a few to many white blood cells, hyaline casts, and much amorphous material and some crystals thought to be uric acid. The blood NPN reached a peak of 175 mg. per 100 cc.; blood uric acid 9.8 mg. per 100 cc.; the blood CO₂ combining power 63 vol. per 100 cc. The spinal fluid was normal and the blood Wassermann negative. His temperature rose from 99° F. during the first 24 hours of symptoms to 101° F. where it remained for a period of 48 hours. About 72 hours after the onset of the previously mentioned symptoms, he began to improve, first with subsidence of the convulsive phenomena and then of the dysarthria or motor aphasia. Within another 24 hour period, his blood pressure had dropped to 125/75 mm. Hg., he talked without any difficulty and muscle tone was entirely normal. He did not appear as alert mentally as he did prior to adenine therapy but he was coherent and oriented. He did not remember what had taken place during the preceding days.

Five days after toxic symptoms appeared, the blood NPN had dropped to 152 mg. per 100 cc. and 4 days later to 90 mg. per 100 cc. It continued to fall to 38 mg. per 100 cc. 30 days after symptoms began. During the first 15 days, the urine specimens contained from a few to many white blood cells, hyaline casts, large quantities of amorphous material and some uric acid crystals. Within 10 days tests for albumin were negative. The highest specific gravity recorded was 1.011.

After adenine was discontinued, therapy consisted of 2 transfusions, intravenous saline and glucose solutions, sodium luminal to control the convulsive phenomena, and folic acid 10 mg. intramuscularly. Eight days after folic acid was started, the reticulocyte count was 5% but a peak count of 15.2% was not obtained until the 14th day of therapy. The white blood cell count remained below 5000 until the 11th day of folic acid therapy when it was 10,900; it remained around this level for 3 days. The red blood cell count and hemoglobin increased very slowly to 2.71 million and 10.1

gm., respectively, 7 weeks after folic acid therapy was started.

During the 10 month period following his discharge from the hospital, he had no recurrence of symptoms and signs. The highest blood pressure recorded was 150/80 mm. Hg.; the blood NPN ranged from 32 to 38 mg. per 100 cc.; the urinalyses were negative for albumin, WBC and RBC, but the highest specific gravity was 1.017. No abnormal eye ground changes or signs of cardiovascular disease, other than firmness and beading of radial arteries, were noted. No evidence of residual central nervous system disturbance could be detected. Fourteen weeks after folic acid therapy was begun, his blood counts were: RBC 4.29 million, Hg. 14.1 gm (92%) and WBC 6400.

Summary of the Case. A 67 year old colored man who has pernicious anemia that responded at one time to liver extract and at another time to folic acid was given 2½ gm. of adenine hydrochloride the first day of therapy and was given 2½ gm. twice a day each of the succeeding 6 days (a total of 32.5 gm.). Evidence of toxicity which began on about the 5th day of therapy consisted of a bad taste in his mouth, anorexia, mental confusion, emesis one time, aphasia, tonic convulsive seizures, transient oliguria, elevation of blood pressure, elevated blood NPN and uric acid and abnormal urinary findings. Progressive improvement began within 72 to 96 hours after adenine was discontinued and he was given therapy consisting of 2 transfusions, intravenous saline and glucose solutions, sodium luminal and folic acid.

Comment and Conclusions. Following the ingestion of large doses of adenine, a patient with Addisonian pernicious anemia in relapse developed uremia. Neither blood regeneration nor any evidence of pellagra developed. These findings are of interest in that they show clearly that acute toxic symptoms arise following large doses of adenine hydrochloride and that no hemopoietic effect was observed. Under the conditions of this study and with recognition of the limitations of a single

case study, it may be stated that the findings do not support Raska's contention that adenine produces blacktongue in dogs but they do support his observation that animals develop nitrogen retention following adenine administration.

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PROTHROMBIN ACTIVITY OF "STORED HUMAN BLOOD"

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THE use of human blood stored in blood banks has almost completely replaced the use of fresh citrated blood or direct whole blood transfusions in the average general hospital today. From *in vitro* studies of "stored blood," many investigators have reported results which show it to be deficient in prothrombin.^{13,14,15} The purpose of this investigation is to determine the degree of prothrombin deficiency found in "stored" human blood. We have undertaken a study on 50 different samples of stored human blood. It is found to be adequate in prothrombin activity upwards of 5 to 7 days.

The toxic manifestations apt to follow the clinical use of the anticoagulants heparin and dicoumarol, require special forms of treatment. The minor bleeding tendencies such as hematuria, ecchymosis and epistaxis can readily be controlled by discontinuing the drugs. If this fails, or when the bleeding is due to heparin overdosage, protamine may be given intravenously.⁶ When dicoumarol is the toxic factor, vitamin K in massive doses (60 to 72 mg.) may be given intravenously. However, gross hemorrhage, and in particular that associated with shock and hepatorenal failure, will not respond to these measures. Dicoumarol hypoprothrombinemia under these conditions is progressive and severe. This situation demands the replacement of whole blood which should contain the normal amount of prothrombin. A similar problem exists in cases of hypoprothrombinemia of hepatocellular origin unresponsive to vitamin K.

In reviewing the literature on the activity of prothrombin in "stored" or "banked blood," we have found varying opinions as to the content of prothrombin remaining; that is to say, the rate of prothrombin conversion at various periods of storage. In some of the "stored blood" studies reported, oxalated blood was used.^{1,13} But, the decalcifying agent used in "stored blood" is sodium citrate. Other reports concern the study of a single specimen. It is apparent that a larger series of "stored blood" should be investigated under actually encountered blood bank conditions, and with the same anticoagulant and preservative which are used today by blood banks in general.

The two common methods used to study prothrombin are: (1) The Warner, Brinkhaus, and Smith, or 2-stage method which extracts the fibrinogen present in the plasma and then converts the prothrombin to thrombin.¹⁷ The final stage occurs with the addition of a constant amount of fibrinogen to the thrombin previously formed, resulting in a fibrin clot. (2) Quick's method and the Link-Shapiro modification of Quick's, which determine the rate of prothrombin conversion.^{11,2} The Warner, Brinkhaus, and Smith method ascertains quantitatively the amount of prothrombin present and may be questioned in a study of this nature. The other constituents such as platelets, thromboplastin, activators and inhibitors are not measured by the 2-stage method. These substances are present in "stored blood" and may alter the prothrombin

activity. The results of the Quick method and the Link-Shapiro modification of it, are affected by the aforementioned constituents.

Investigators using the Warner, Brinkhaus, and Smith method on several bloods, found a diminution in the amount of prothrombin present as follows: blood stored 9 to 12 days—75 to 91 % of normal;^{10,13} 18 to 25 days—50 to 61 % of normal;^{10,18} and by the 37th day, 40 % of normal.¹⁹ Those using Quick's method on a somewhat greater number of blood samples found a wide variation in the speed of prothrombin conversion. Oxalated blood stored 24 hours, 50 % of normal.¹³ Citrated blood stored 1 to 3 days—35 to 73 % of normal;^{10,14} On the 7th day, 25 to 55 % of normal;^{14,15} 9 to 13 days—20 to 50 % of normal;^{14,15} 8 to 24 days—14 % of normal;¹⁰ 28 to 38 days—50 % of normal.³ The wide variation resulting from Quick's method makes it difficult to arrive at a definite conclusion as to the activity of prothrombin in "stored blood."

We have undertaken the investigation of 50 units of "stored blood" selected at

random. Each unit was examined daily during a period of 21 days. At this hospital blood is considered suitable for transfusion for 21 days.

Method. From each of 50 healthy donors 500 cc. of blood was obtained. Each unit was thoroughly mixed with 125 cc. of acid-citrate-dextrose solution following the usual blood bank technique. Acid-citrate-dextrose solution has been reported as being the best preservative for whole blood.⁵ Seventy per cent of the cells so preserved survive after 35 days and 65 % after 39 days of storage.⁵ Under aseptic precautions 18 samples, 4 cc. each, were transferred immediately to rubber-capped, sterile vacuum tubes. The specimens were stored at 4° C. \pm in the blood bank refrigerator. An equal vacuum was used for the tubes and the donor storage bottles.

The technique of Link-Shapiro modification of Quick's method, using rabbit lung as the source of thromboplastin was used.² The thromboplastin used gave an average whole plasma prothrombin time of 12.4 seconds. An original lot of thromboplastin and chemicals was used throughout this study. The same technician performed all determinations. The whole plasma prothrombin time and 12.5 % plasma prothrombin time (made

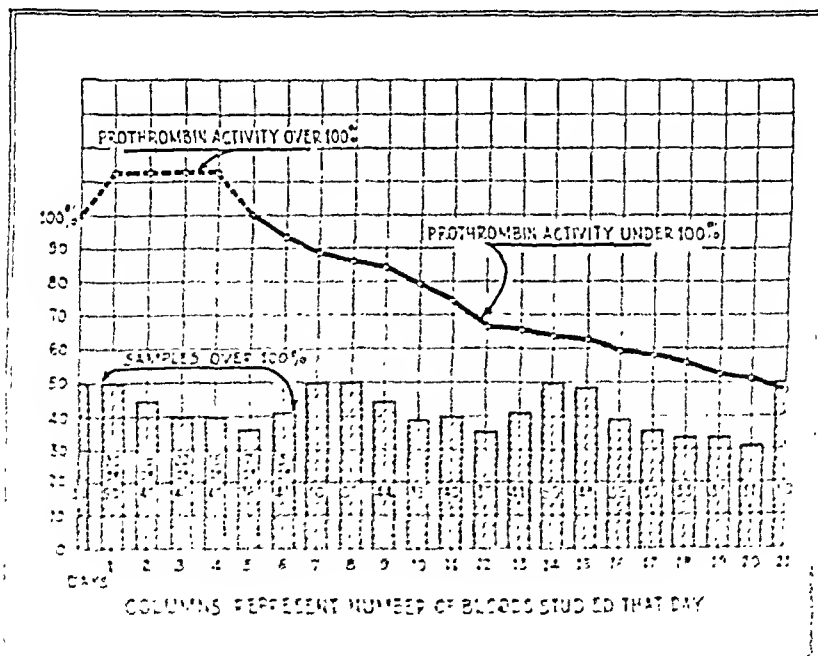


FIG. 1. Whole plasma prothrombin activity.

by diluting whole plasma with physiologic saline) were performed on each individual blood sample daily with the exception of a few. This may be noted in Figures 1 and 2. The error allowed for whole plasma is 0.5 second and for the 12.5% plasma, 1 second. It is believed by some that 12.5% plasma is more sensitive than whole plasma to minute changes in prothrombin and is therefore a more sensitive indicator of the rate of prothrombin conversion.¹⁶

On the day each blood was taken an individual dilution curve (graph) was made with physiologic saline and plasma according to the method outlined by Quick.¹² From these graphs the percentage prothrombin activity was read for each individual subsequent determination of whole plasma prothrombin time.

Results. The percentage prothrombin activity of whole plasma may be seen in Figure 1 for each day. It can be noted that the prothrombin activity is over 100% for the first 4 days following storage and 100% for the 5th day. However, a few continued to show over 100% activity through the 6th day. After the 5th day there is a gradual drop of prothrombin activity to 84.8% on the 9th day, followed

by a more rapid drop to 66.2% on the 12th day, after which the drop is gradual again to 47.7% by the 21st day. Any possible increase in activity over 100% cannot be expressed numerically during the first 4 days, as the curve of prothrombin activity is maximum at 100%. For these 4 days the whole plasma prothrombin time is shorter (more active) than on the day the blood was drawn.

The 12.5% plasma, as demonstrated in Figure 2, shows a somewhat similar change in the rate of prothrombin conversion, although not quite as dramatic. For the first 5 days following storage of whole blood there is a decrease in the dilute prothrombin time (increased prothrombin activity) beyond the limit of technical error. On the 6th and 7th days there is no change in dilute prothrombin time as compared to the day the bloods were taken. From the 8th to the 21st day there is a slow rise in the dilute prothrombin time.

Discussion. Crosbie *et al.* found an increased coagulability of "stored blood" during this same period;³ Banfi *et al.* and

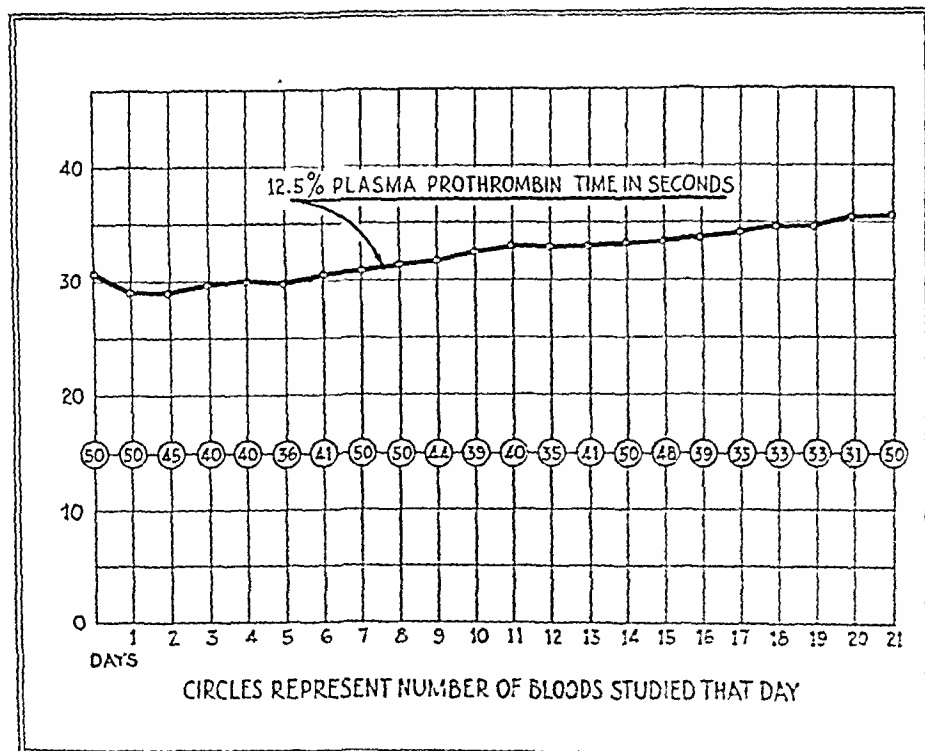


FIG. 2.—12.5% plasma prothrombin time.

Kolmer found increased prothrombin activity within 24 hours of storage.^{1,8}

Thromboplastin is essential for the mechanism of prothrombin conversion as well as ionizable calcium. Crosbie *et al.*, Drew *et al.*, and Kolmer have shown that platelets begin to disintegrate in "stored blood" within 24 hours and continue to disintegrate for 5 or 6 days.^{3,4,8} As platelets disintegrate thromboplastin is liberated. The excess thromboplastin is probably responsible for the more rapid prothrombin conversion as illustrated in both the whole and dilute plasmas during the first 4 to 5 days, respectively.

Lord, Andrus, and Moore demonstrated in dogs and *in vitro* that, "the changes in the total content of prothrombin in the plasma of a recipient after a transfusion are dependent on the prothrombin content of the plasma of the donor, and may be calculated on the basis of addition."⁹ The amount of prothrombin contained in 500 cc. of blood is relatively small when compared with the total quantity of prothrombin in the normal human. Theoretically, a single transfusion should have little effect upon the prothrombin present in the recipient. However, Karabin *et al.*

have observed several instances where a marked improvement occurred in cases of hypoprothrombinemia following the use of "stored blood."⁷

The results reported in this investigation are from *in vitro* determinations of the activity of prothrombin in "stored blood." It cannot necessarily be concluded from this experiment that the use of "stored blood" during the period of hyperprothrombin activity introduces hypercoagulable factors in the recipient.

Conclusions. (1) Prothrombin activity or rate of prothrombin conversion in "stored" or "banked blood" is increased during the first 4 to 5 days and is normal from the 5th to the 7th day. The increased prothrombin activity during the first few days of storage is probably due to the disintegration of platelets which liberate thromboplastin. Thereafter, the prothrombin activity slowly falls to 47.7% by the 21st day.

(2) It is practical to use "banked blood" for hypoprothrombinemia, or bleeding associated with it, as an agent containing normal hemostatic qualities, during the first week of storage.

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THE SIGNIFICANCE OF THE PAUCITY OF SICKLE CELLS IN NEWBORN NEGRO INFANTS

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SINCE the sickle cell trait is inherited as a Mendelian dominant in negroes²⁴ and is therefore presumably present from the onset of hematopoiesis in fetal life, sickle cell disease should occur in infancy as often as later in life. Although McGavack and Nussbaum³¹ found that 50% of 214 reported cases had symptoms of their disease before the age of 2 years, there are very few cases reported before the age of 6 months. Graham and McCarty²⁰ report the autopsy of a 4 month old negro infant who died of bronchopneumonia, whose spleen was said to show typical findings of sickle cell disease. Wollstein and Krcidel⁴⁶ mention death due to bronchopneumonia in a 3 month old baby with sickle cell disease. Unfortunately clinical data are lacking in both these cases. Tomlinson⁴⁰ reports that sickle cell anemia was found at autopsy in 2 cases in the age group of 1 to 6 months in his investigation made at the Canal Zone. We have found two other reports^{10,25} in the literature of hospital admissions for sickle cell disease before the age of 6 months, and six others^{2,7,11,12,13,30} in the succeeding age period of 6 months to 1 year. The paucity of cases in infancy is surprising in view of the frequency of hospital admissions in later childhood. Several of our patients have had more than 20 periods of hospitalization for the management of their crises. However, there have been several cases in older children^{5,21,22,35,46} where there was a history of symptoms beginning at the age of 6 to 12 months. Often the story is given

of being "sickly as long as I can remember," but the exact data for infancy is not known.

In a study of the baby of one of our sickle cell anemia patients, we found only 6% sickling at birth, with a gradual increase to 90% at 4½ months. When last seen at 6 months he was still well and had no hematologic evidence of sickle cell anemia. In 26 reported deliveries of patients with sickle cell disease, sickling was noted to be present in 8 of the infants,^{23,27,28,36,37,39} but the percentage of sickled red cells was mentioned only once,²⁹ in which case it was given as 1%. Sharp and Schleicher³⁴ report a baby in whom no sickling was found at birth, but in whom sickling was found to be present at the age of 4 months. The largest study of sickling in newborn negroes was done by Diggs and co-workers,¹⁶ who found sickling in 6 out of 159, a percentage of 3.8. This is considerably lower than their over-all figures of 8.3% for 2539 negroes of all ages. Although the percentage of sickled red cells in each preparation was not noted, the comment was made that sickling in newborns was "less marked and developed more slowly than in adults with the trait." Graham and McCarty¹⁹ found sicklemia in 5 out of 6 newborn infants of mothers with sicklemia. Beck and Hertz⁴ found sicklemia in 1 out of 5 newborns tested, and stated that there was only 5% sickling in the sealed preparation. Since the red cells of adults with the trait are known to sickle 100%, the scattered evidence presented seems to indicate that

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sickling is incompletely developed at birth.

Given a newborn who shows the sickling trait, there is at present no certain method for predicting whether he will later develop the disease; for it is not known whether the means of differentiation (all of which depend upon differences in sickling threshold to oxygen tension^{35,44}) are valid at that period. Genealogical studies have not been very helpful, since the attractive theory that homozygosity might be responsible for the disease, in contrast to heterozygosity for the trait, is not well supported factually.³² In view of the generally accepted estimate that, of the 7.3% of negroes who have sickle cell anemia, only 1 out of 40¹⁶ will have the disease, it is not statistically profitable to make a study of negro newborns in the hope of finding one who will develop sickle cell disease. Indeed, there are no records of cases of sickle cell anemia which have had careful hematologic studies since birth. However, it seemed possible that the study of sickle cell anemia in the newborn negro infant might indirectly throw some light on the problem of the development of sickle cell disease.

Methods. Sickle cell preparations were made on 226 consecutive negro newborn infants in the nursery of Kings County Hospital. The mothers on the maternity service were used as the control series.* Finger blood from the mothers and heel blood from the infants was used. The standard sealed preparation¹⁵ was made, using clean glass slides and No. 1 cover slips. For the first few cases a vaseline seal was used, but subsequently paraffin was substituted because it eliminated the tendency for the blood to retract at the edges of the cover slip. All preparations were made in duplicate, incubated at 37.5° C., and read for sickling at 24 hours. Only the typical sickled cells with long bizarre processes were counted, doubtful cells of odd shapes being excluded. The percentage of sickled cells was determined from counting 200 red blood cells in the areas which showed maximum sickling. Pressing too hard on the cover slip was found to favor disintegration of the

sickle cells; in infant blood with macrocytic red cells and tendency to the formation of thicker drops, it was particularly important to avoid this pressure when making the sealed slide. Sickling preparations are notoriously capricious^{17,20,35} so that consistent procedure in the smallest detail is of the utmost importance. It is realized that determining the percentage of sickled cells does not yield exactly the same figure in each preparation made from a given sample, but differences of the order of 10 to 20% can be interpreted as being significant. It was found that the blood of the newborns sometimes required 48 hours to reach maximum sickling, so that the percentage of sickling was noted at 24, 48, and 72 hours. At 72 hours the sickling usually had not increased, but had begun to diminish, and often partial hemolysis had set in; these figures are therefore not included in this paper. In the case of the mothers, maximum sickling occurred within the first 24 hours.

The hemoglobin values of the mothers were obtained from their charts. The Haden-Hausser method was used.

Results. Of the 226 negro mothers examined, 18 (8%), showed sickle cell anemia; the data on them is presented in Table 1. None had clinical or hematologic evidence

TABLE 1.—MOTHERS WITH SICKLE CELL ANEMIA (18 OUT OF 226 CASES)

Case No.	Age, years	Hgb, gm. %	Sickling % at 24 hrs.
1	19	10.5	96
5	21	10.0	100
8	19	10.0	84
18	27	9.0	100
52	31	.	100
67	28	9.5	100
116	19	10.5	100
121	21	8.5	100
123	17	11.0	100
128	22	9.0	100
130	18	10.5	100
140	15	9.5	63*
143	21	10.0	86*
155	27	10.0	92
167	22	10.5	94
179	22	11.0	100
180	22	10.5	95
220	19	10.0	100

* Read at 72 hours.

of sickle cell disease. The percentage of sickled red cells was usually 100%, and at 24 hours exceeded 84% in every case.

* We are indebted to Dr. C. A. Gordon of the Long Island College Division of the Obstetrical Service and to Drs. E. E. Smith and Dr. J. S. Bick of the Long Island College Division of the Pediatric Service of Kings County Hospital for their kind permission to study their patients.

Of the 226 infants examined, 19 (8.4%), showed sicklemlia (Table 2). The case numbers in the table are the same as those of the corresponding mothers except for

TABLE 2.—NEWBORNS WITH SICKLEMLIA (19 OUT OF 226 CASES)

Case No.	Age, days	Sickling		Sicklemlia in mothers
		% at 24 hrs.	% at 48 hrs.	
4a	3	2 0	..	No
5a	2	4 0	..	Yes
24a	2	0 5	..	No
35a	3	1 0	1 0	No
37a	3	1 0	8 5	No
40a	1	1 0	7 0	No
67a	1	5 0	..	Yes
85a	2	8 5	11 0	No
116a	1	2 5	4 5	Yes
128a	1	1 5	1 5	Yes
129a	1	2 5	19 0	No
153a	2	19 0	19 0	No
154a	3	14 5	20 5	No
155a	2	12 5	15 0	Yes
167a	1	19 5	19 5	Yes
179a	1	3 5	..	Yes
180a	2	12 5	21 0	Yes
181a	1	29 5	29 5	No
220a	1	16 5	29 0	Yes

the addition of the letter "a." Maximum sickling varied from 0.5 to 29.5%, with a mean of 11%. The tendency for the last figures to be higher may be accidental or may be due to improved technique. In 6 instances blood was also sickled by the gas chamber method of Halin and Gillespie,²¹ and the percentage of sickled erythrocytes was found to be essentially the same as that of the sealed preparation. The infants with sicklemlia were all healthy full term babies.

Discussion. The incidence of sicklemlia in the newborn negroes in our series agrees very well with that of the mothers, being 19 and 18 respectively out of 226 (8.4 and 8%). These figures compare closely with the usual figure quoted for this country—7.3% of a series of 8423 negroes.¹⁶ Of the 19 babies with sicklemlia, 9 had mothers with the trait—a figure which would be expected for a Mendelian dominant characteristic.²⁴

Despite the fact that the incidence of sicklemlia of the infants and adults was almost identical in both groups two important differences with respect to the sickling were noted. First, the sickling

of the infants' red cells often required 48 hours to reach a maximum instead of the 24 hour period required for the mothers' red cells. This presumably means that a lower oxygen tension²¹ is required for the sickling of the infants' cells. It has been shown that there is a significant shift to the left of the oxygen dissociation curve of oxyhemoglobin at birth, which gradually reaches adult values at the age of 6 weeks.¹⁴ The presence of fetal hemoglobin might then explain the longer period necessary for the sickling of newborn red cells.

The second difference noted was that, of the mothers who had sicklemlia, the red cells showed 84 to 100% sickling, in contrast to those of the infants which showed only 0.5 to 29.5% sickling. The greater affinity of fetal hemoglobin for oxygen should not account for the low percentage of sickled red cells in newborns with sicklemlia, since the maximum percentage of sickling could not be raised over that of the sealed preparation by use of the gas chamber method where oxygen can be excluded entirely from the system.

It might be thought that immaturity of many cells in the newborn would reduce the sickling tendency, as there are in the literature reports that normoblasts and even reticulocytes fail to sickle. Careful study¹³ has shown that, while the velocity of sickling may be retarded in immature cells, the percentage is the same as in older ones. The blood of these infants contained no high percentage of immature cells and another explanation must be sought.

It is well established that human fetal hemoglobin differs chemically from adult hemoglobin. Differences have been demonstrated with respect to alkali denaturation,⁶ histidine content,⁴² immunological properties,¹⁵ the oxygen dissociation curve,¹¹ crystallization,³³ and sedimentation constants and electrophoretic mobilities.¹ It is thought that these differences are due to variation in the chemical structure of globin, especially since spectroscopic analyses have failed to show

differences in the prosthetic group of hemoglobin.²⁶ Brinkman *et al.*⁸ have shown that newborn blood contains about 80% of the fetal alkali resistant hemoglobin. This was still present in two infants 3 months old, but was absent in one of 7 months.⁹ Trought⁴¹ in a similar investigation found that it disappeared as early as 4½ months. The theory that at once presents itself is that fetal hemoglobin is unable to produce sickling, and that the sickling trait progressively becomes 100% with the gradual formation of the new red cells containing the adult type of hemoglobin which possesses the sickling property. This hypothesis is further strengthened by the fact that the estimated life span of the erythrocyte is 4 months.⁴⁵ This fits in well both with Trought's observation that the fetal hemoglobin disappears at 4½ months and with our finding of an infant who developed 90% sickling at 4½ months in comparison with the 6% sickling at birth. Whether this last instance represents the usual course of events can be decided only by following the percentage of sickle cells from birth through one year in a series of infants, a study now under way.* Whether the sickling in infancy follows a different pattern in those infants who will develop anemia and in those merely showing the trait will take some years to determine.

Since an oxygen tension of 45 mm. Hg. is taken to be the threshold for sickling in patients with sickle cell disease,²⁵ the much lower oxygen tension that occurs *in utero*⁷ should cause complete sickling and thus be incompatible with life. In fact, if the same low tension of 16 mm. is achieved in the human fetus as in the sheep, sickling *in utero* should occur even in those with the sickling trait only, since the oxygen tension threshold in these cases is estimated to be 18 mm.²⁵ However, we could find no cases in the literature of

pathologic findings of sickle cell anemia in autopsies of newborns and stillbirths. The youngest autopsied cases were infants 1 month,¹⁰ 3 months,²⁵ and 4 months²⁰ old, the first being complicated by acute otitis media, and the last two by bronchopneumonia. It seems likely then that fetal hemoglobin lacks the sickling properties of adult hemoglobin, thereby preventing automatic extinction of sickle cell disease from deaths *in utero*, and partially protecting the infant in the first 4 months of life during which time it gradually disappears from the blood.

Summary. 1. A study was made of sickling in 452 consecutive negro newborns and their mothers: 8% of the mothers and 8.4% of the infants showed sicklelema.

2. The red cells of mothers with sicklelema showed 84 to 100% sickling, while those of the newborns showed only 0.5 to 29.5%. The red cells of the latter also required a longer time to attain maximum sickling.

3. It is suggested that these differences are due to a chemical difference between fetal and adult hemoglobin because:

(a) Fetal hemoglobin as tested by the alkali denaturation method differs from adult hemoglobin and does not disappear from the blood until 4½ months. The oxygen dissociation curve of fetal hemoglobin is shifted to the left.

(b) The life span of the erythrocyte is about 4 months. If adult hemoglobin begins to be manufactured at birth, 4 months would elapse before it would entirely replace fetal hemoglobin.

(c) In one case of sicklelema followed from birth, sickling increased progressively from 6% at birth to 90% at 4½ months.

4. The absence of death *in utero* from sickle cell anemia may be due to the protective influence of fetal hemoglobin which is unable to sickle even at the low oxygen tension which exists in the fetus.

* Since this paper was submitted for publication, 11 infants with sicklelema have been followed for 4 months at monthly intervals since birth. Sickling increased progressively to reach an average of 60% at the age of 4 months.

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THE LEUKOCYTOSIS OF DIABETIC ACIDOSIS

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LEUKOCYTOSIS is of common occurrence in diabetic acidosis.^{1,2,3,7} It is generally polymorphonuclear in type. Allan^{1,2} first pointed out that its occurrence is apparently independent of the presence or absence of intercurrent infection. Rather extreme leukocyte levels are sometimes seen. Root⁸ reports a white count as high as 92,000 in diabetic coma, and Anderson³ reports a white count of 97,000. Heck and Hall⁶ state that diabetic acidosis is sometimes accompanied by a leukemoid reaction, with young leukocytes, myelocytes and even myeloblasts appearing in the peripheral circulation.

Working with experimental anisotonia in animals, it was recently shown¹¹ that a selective polymorphonuclear leukocytosis regularly accompanied the induction of extracellular hypertonicity. The increased concentration/mm.³ of absolute numbers of circulating neutrophils was roughly proportional to the increase in milliosmolar strength of the serum. The hypothesis was advanced that under certain conditions, hypertonicity of the extracellular fluids might be an important contributing factor for the production of polymorphonuclear leukocytosis.

It was the purpose of the present study to observe the levels of hypertonicity naturally occurring in the course of diabetic acidosis and see if they bore any relationship to the extent of leukocytosis which accompanied it.

Methods. Seven consecutive diabetic coma patients at the New England Deaconess Hospital were studied. Levels of hypertonicity were determined by freezing point depression measurements on deproteinized blood samples and are reported in milli-

osmoles per liter.* Absolute neutrophil counts were determined by total white counts and concurrent differential counts on 500 cells. All white blood cell counts were previously corrected for hemoconcentration by observing the variation in hematocrit values between coma and recovery.

Levels of tonicity of the serum were recorded at the height of coma, 6 hours later, and following return to a "normal" status. Absolute neutrophil levels were recorded at the height of coma, 20 hours later and following return to a "normal" status.

Results. The data obtained is presented in tabular form in Table 1.

In each case a substantial level of hypertonicity was recorded during the height of coma. Similarly, a substantial level of leukocytosis was recorded during the height of coma. The increases in count were accompanied by a "shift to the left" in the Schilling hemogram, with immature polymorphs and, on two occasions, myelocytes appearing in the circulation. If one plots the absolute neutrophil counts obtained at the height of coma against the concurrent hypertonicity of the serum it will be seen that they bore a direct proportionality to one another (Fig. 1).

All points fell close enough to a straight line relationship to be within the range of experimental error, excepting one. In that instance an absolute neutrophil count of 20,000 was considerably higher than would have been anticipated from the molarity of the patient's serum alone. It is of interest that in that instance a concomitant infectious element may have been present as the patient was under observation for acute appendicitis. No correlation existed between the level of

* Conversion factor: $1 \text{ mOsm} = 1.86 \text{ M}$.

TABLE I.—ANALYTICAL DATA

Analysis	Patient	Time										Return to normal*		
		Coma	6 hr. post coma					20 hr. post coma						
Molarity milliosmoles /l.			SEG.	STAB.	MYL.	E. L.	M.		SEG.	STAB.	MYL.	E. L.	M.	
W. B. C.	V. L.	381												
	M. H.	370	322											328
	P. McG.	392	355											301
	L. D.	344	370											339
	E. R.	355	322											306
	L. P.	360												322
M. L.		406												306
	V. L.	26,760												319
	M. H.	19,080												
	P. McG.	21,850												
	L. D.	18,700	10,000											
	E. R.	24,350												
M. L.	L. P.	20,020												
		22,720	15,520											
Smear	V. L.	SEG.	STAB.	MYL.	E. L.	M.		SEG.	STAB.	MYL.	E. L.	M.		
	M. H.	62	20	0	0	18	0							
	P. McG.	83	3	0	0	9	5							
	L. D.	80	6	3	0	9	2							
	E. R.	71	12	0	0	14	3							
	L. P.	81	8	2	0	8	1							
	M. L.	80	14	0	0	4	1							
		82	5	0	0	13	0							
	V. L.	55												
	M. H.	52												
	P. McG.	49												
	Hematocrit vols. %	L. D.	51											
E. R.		39												
L. P.		44												
M. L.		44												
V. L.		5	7											
M. H.		9	11											
P. McG.		14												
L. D.		4												
E. R.		9												
L. P.		5												
M. L.		5	7											
CO ₂ m M/l.		V. L.	728	185										
	M. H.	305	105											
	P. McG.	450	123											
	L. D.	383	233											
	E. R.	390	151											
	L. P.	445	250											
Bl. sugar mg. %	M. L.	910	452											
	V. L.	728	185											
	M. H.	305	105											
	P. McG.	450	123											
	L. D.	383	233											
	E. R.	390	151											
M. L.	L. P.	445	250											
	M. L.	910	452											
	V. L.	728	185											
	M. H.	305	105											
	P. McG.	450	123											
	L. D.	383	233											
M. L.	E. R.	390	151											
	L. P.	445	250											
	M. L.	910	452											
	V. L.	728	185											
	M. H.	305	105											
	P. McG.	450	123											
M. L.	L. D.	383	233											
	E. R.	390	151											
	L. P.	445	250											
	M. L.	910	452											
	V. L.	728	185											
	M. H.	305	105											
M. L.	P. McG.	450	123											
	L. D.	383	233											
	E. R.	390	151											
	L. P.	445	250											
	M. L.	910	452											
	V. L.	728	185											
M. L.	M. H.	305	105											
	P. McG.	450	123											
	L. D.	383	233											
	E. R.	390	151											
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M. L.	V. L.	728	185											
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M. L.	L. P.	445	250											
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	E. R.	390	151											
	L. P.	445	250											
	M. L.	910	452											
M. L.	V. L.	728	185											
	M. H.	305	105											

* 1-3 weeks post coma

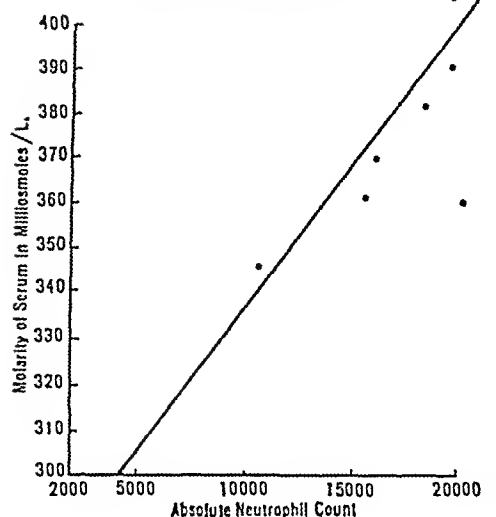
RELATION OF MOLARITY OF SERUM TO
ABSOLUTE NEUTROPHIL COUNT

FIG. 1.

absolute neutrophil count and molarity of the serum, once the period of recovery ensued. In general, a relative leukopenia and neutropenia was common for a month or more after recovery from coma.

It is of interest that no eosinophils were seen in any blood smear during coma.

Discussion. Although a proportional fluctuation in the molarity of the serum and absolute numbers of circulating neutrophils does not, of itself, imply a cause and effect relationship, it would seem, in view of the previously reported experimental relationship,¹¹ and in view of the close proportionality observed in

this series of cases, that such a possibility is worthy of consideration.

The exact mechanism of such a hypertonic-leukocytosis would remain to be defined, but would seem to be an effect of the hypertonicity *per se* rather than an effect of increased concentration of any one or more of the elements comprising the hypertonicity. The experimentally induced hypertonicity was essentially an increased concentration of Na^+ and Cl^- , whereas the reverse obtains in the hypertonicity of diabetic coma. As repeatedly shown by Sunderman,^{9,10} Atchley, Loeb, *et al.*,⁴ Danowski, Winkler and Peters⁵ and others, there is a lowering of plasma Na^+ and Cl^- levels in diabetic acidosis. The hypertonicity of diabetic coma is essentially an increase in the organic constituents of the plasma: sugar, urea and ketone bodies. Thus, if the same process incites the leukocytosis in both instances it would imply an effect of the hypertonicity itself, rather than effect of the elements which comprise it.

Summary. Seven cases of diabetic acidosis are presented, in which studies were made on the simultaneous fluctuations in molarity of the serum and absolute numbers of circulating neutrophils.

The hypothesis is advanced that the hypertonicity of the plasma in diabetic acidosis may play a causative rôle in the concomitant leukocytosis.

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BENIGN IDIOPATHIC SPONTANEOUS PNEUMOTHORAX

A REVIEW OF 63 CASES*

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In 1943 the United States Army had 873 hospital admissions for simple benign idiopathic spontaneous pneumothorax.⁴ In recent years it has become apparent that idiopathic spontaneous pneumothorax is relatively common. Kjaergaard² studied 51 cases admitted to the hospitals of Denmark in a 20 year period. Perry⁶ found 85 cases in the London Hospital record in a 14 year period. Ornstein and Lereher⁵ reported a study of 58 cases. Blackford¹ reviewed 15 cases in college students at the University of Virginia. Leach³ reported 126 cases from the Army Air Forces. Niehaus⁴ reported 24 cases. Benign idiopathic spontaneous pneumothorax occurs most often in healthy young adult males. Pleural fluid is slight or absent. Fever is uncommon. Uncomplicated reexpansion is the rule, but recurrence is not infrequent. The chest roentgenogram is negative for infiltration. The usual explanation for spontaneous pneumothorax is the rupture of alveolar walls with air dissecting its way along interstitial bands to the pleura, and causing the formation of a bleb. This bleb has a check valve, allowing the entrance, but not the egress of air, with resultant ballooning, thinning and rupture of the bleb. It is important that the benign nature of idiopathic spontaneous pneumothorax be recognized and that pulmonary tuberculosis not be incriminated.

This report, based on 63 cases, is a clinical study of 2 groups of patients, 1

group of 27 studied in Los Angeles, and the other group of 36 patients seen at Bellevue Hospital in New York. The material is best presented under several headings.

AGE OF PATIENT. The youngest patient was 18; the oldest was 62 years of age. Seventy-five % of patients were under 40 years of age, and almost 50% were between 20 and 30 years. Thus, benign spontaneous pneumothorax is primarily a disease of young adults (Table 1).

TABLE 1.—AGE OF 63 PATIENTS WITH SPONTANEOUS PNEUMOTHORAX

Age	No.
18-20	4
21-30	30
31-40	13
41-50	10
51-60	4
61-62	2

SEX. In the Los Angeles group only males were examined. In the Bellevue Hospital group there were 30 males (26 white, 4 colored), and 6 females (5 white and 1 colored). The ratio of males to females was 5 to 1.

SIDE OF PNEUMOTHORAX. In most studies the spontaneous pneumothorax was more often on the right side. In our studies, 31 patients had a right pneumothorax and 32 a left. Right and left side appear to be affected equally.

TIME FOR REEXPANSION (Table 2). In almost 70% of patients the time for reexpansion was 7 weeks or less. In the individual patient it was difficult to pre-

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TABLE 2.—TIME FOR REEXPANSION IN 57 CASES OF SPONTANEOUS PNEUMOTHORAX

Weeks	No.
1	3
2	3
3	8
4	8
5	8
6	6
7	9
8	7
9	1
10	1
11	0
Over 11	3

diet the time for reëxpansion. Leakage of air into the pleural space may continue for days, and even weeks. Of 3 patients who had 15% collapse, 1 required 26 days, the second 7 days, and the third 50 days for reëxpansion. One patient had a 50% collapse on admission with gradually increasing collapse to 90% in a period of 2 weeks, and then uncomplicated reëxpansion. Another patient "blew out" again on the 9th hospital day, and then had an uncomplicated reëxpansion. One patient required 100 days to reëxpand his collapsed lung. Air samples on the 56th hospital day were consistent with a diagnosis of bronchopleural fistula.

ETIOLOGY. Five patients gave a history of bronchial asthma. None, however, had an asthmatic attack at the time of the pneumothorax. In 58 patients the cause was not apparent and was therefore labeled idiopathic. It was noted that almost every patient was thin and underweight. Several patients were of normal weight. None was overweight or obese.

HISTORY OF EFFORT. In only 2 patients (3%) did the onset of symptoms occur during or just after effort. One patient had thrown a football, and another was straining at stool. Four patients were aroused from sleep. A history of effort associated with the onset of symptoms was rare, and apparently coincidental.

CHEST PAIN. Chest pain occurred in 62 patients, or almost 100% of cases. This pain was usually described as "sharp" and "cutting," rarely as "dull," and was always on the side of the pneumothorax. Frequently the pain was pleuritic and

lasted from 1 to 4 days. Benign spontaneous pneumothorax may be completely asymptomatic. One patient had a right pneumothorax with sudden pain in 1938. On a routine clinic visit 1 year later she was found to have a 10% collapse of the right lung. She was completely asymptomatic. Two patients, not included in this series, also had asymptomatic spontaneous pneumothoraces. One patient was admitted with severe urticaria. On routine fluoroscopy she was found to have a spontaneous pneumothorax. Another patient had a transverse myelitis and persistent fever. A chest film showed 50% collapse of the right lung. Wilson⁷ found 5 cases of spontaneous pneumothorax without symptoms on routine chest Roentgen rays of Yale students in a 4 year period.

DYSPNEA. Fifty-two patients (83%) had slight to marked dyspnea. It was difficult to correlate the degree of collapse with the severity of the dyspnea. One patient with 70% collapse and another with 60% collapse gave no history of dyspnea. One patient with almost 100% collapse of the left lung had moderate dyspnea, whereas 2 young adults with a 5% collapse also had moderate dyspnea. Several patients had increasing dyspnea during the first few days. As a group, however, the greater the degree of collapse, the more severe the dyspnea.

PLEURAL ADHESIONS. In benign idiopathic spontaneous pneumothorax, the chest roentgenogram reveals no infiltration either at time of lung collapse or when the lung is reëxpanded. In this study no patient had pleural adhesions demonstrable by chest roentgenogram. In Ornstein's group, the 3 patients who had adhesions developed active pulmonary tuberculosis within 3 years. Of 25 consecutive unselected patients admitted to the chest service of Bellevue Hospital with active pulmonary tuberculosis and a spontaneous pneumothorax, 24 had pleural adhesions demonstrable on Roentgen ray. The presence of adhesions with a spontaneous pneumothorax calls for careful clinical

study and continued observation for a possible tuberculous cause.

CYANOSIS. Five patients (8%) were slightly cyanotic at the onset. These patients had moderate to marked dyspnea, and 4 had over 50% lung collapse.

PLEURAL FLUID. Forty patients (65%) had no pleural fluid; 23 patients had pleural fluid, enough to blunt the costophrenic angle in 19, to the level of the diaphragm in 2, and above the diaphragm in 2. The 2 patients with fluid above the diaphragm had thoracenteses, and "pure blood" was aspirated. One patient continued to reaccumulate fluid which became more serous and then ceased after 6 weeks. After 3 years, this patient is in good health. In 25 unselected consecutive patients with active pulmonary tuberculosis and spontaneous pneumothoraces, 13 had fluid above the level of the diaphragm. In idiopathic spontaneous pneumothorax, the accumulation of appreciable amount of fluid, that is above the level of the diaphragm, is unusual, and in such cases the possibility of underlying pulmonary tuberculosis or other pulmonary disease must be considered.

SEDIMENTATION RATE. In 22 patients the sedimentation rate was normal. It was slightly elevated in 8 and was not determined in 35 patients, on admission. In benign idiopathic spontaneous pneumothorax a normal or slightly elevated sedimentation rate is usual.

LEUKOCYTE COUNT. On admission, 21 patients had normal white blood cell counts and 9 patients had slight to moderate elevation of the leukocyte count. These quickly returned to normal, unless there was another explanation for the leukocytosis. (The white blood cell count was not determined on the remaining patients on admission.)

FEVER. Seven patients had a low fever lasting 1 week or less. One patient had fever for 1 month, but he developed thrombophlebitis of the leg soon after admission. Another patient was afebrile for 3 weeks and then had fever for 2 weeks during which time he had clinical evidence

of a leg thrombophlebitis. Ordinary uncomplicated cases of spontaneous pneumothorax were unaccompanied by fever lasting more than a few days. If fever persists, another explanation must be sought. If none is found, the spontaneous pneumothorax should not be regarded as benign.

TREATMENT. The patient is kept at bed rest until the collapsed lung has reexpanded. Bathroom privileges are permitted when the lung has reexpanded to about 80 or 85% of its volume. Following complete reexpansion, the patient is allowed full activity and a return to normal life. In case of positive pressure pneumothorax, due to a ball-valve type of action, aspiration of air or temporary tidal drainage is indicated. No case in this series had this complication.

RECURRENCE. Nineteen % of patients had recurrent pneumothoraces. Ten of such patients had collapse of the same lung, and 2 had collapse of the opposite lung. Three patients had 1 recurrence, 5 had 2 recurrences, 2 had 3, 1 had 4, and 1 had 6 recurrences.

FOLLOW-UP. Eighteen patients had careful and adequate study with serial chest roentgenograms for from 1 to 8 years following their idiopathic spontaneous pneumothoraces. All were found to be in good health and none had any evidence of tuberculosis.

Summary. A clinical study of 63 patients with benign idiopathic spontaneous pneumothorax is presented. The following were noted: 1. Half of the patients were between 20 and 30 years of age. The ratio of males to females was 5 to 1.

2. Half of the pneumothoraces were on the right side and 50% on the left.

3. In 70% of patients the time for reexpansion was 7 weeks or less. In the individual patient it was difficult to predict the time required for reexpansion.

4. In only 2 patients (3%) did physical exertion precede the onset of the spontaneous pneumothorax.

5. Chest pain occurred in 62 patients (almost 100%) and subsided in a few days.

6. Dyspnea was present in 52 patients (83%).

7. Five patients (8%) were slightly cyanotic at the onset.

8. Forty patients (65%) had no pleural fluid. Two patients had fluid above the diaphragm, and in both "gross blood" was aspirated.

9. No patient had pleural adhesions demonstrable on chest roentgenogram. This is in sharp contrast to a study of 25 patients with active pulmonary tuberculosis and spontaneous pneumothorax in whom 24 had demonstrable pleural adhesions, and 13 had fluid above the level of the diaphragm.

10. The sedimentation rate was normal in 73% of the group of patients in which this was performed, and slightly elevated in 27%.

11. Of those patients having white blood cell counts on admission, 70% were nor-

mal and 30% showed slight to moderate elevation.

12. Only 7 patients had a low fever lasting 1 week or less. The other patients were afebrile. Two patients had fever lasting more than 1 week, and both had thrombophlebitis of a leg.

13. Recurrences occurred in 19% of the patients, usually on the side of the previous collapse.

Conclusions. Benign idiopathic spontaneous pneumothorax occurs most often in young healthy adult males. Fever and elevation of the white blood cell count and sedimentation rate, if present, are slight and transient. Pleural adhesions and appreciable amounts of pleural fluid other than "gross blood" from pleural tears, are very unusual and should arouse the suspicion of underlying pulmonary tuberculosis or other disease of the lungs. The prognosis of benign idiopathic spontaneous pneumothorax is excellent and uncomplicated reëxpansion is the rule.

We wish to express our gratitude to J. Burns Amberson, Jr. M.D., for helpful suggestions and criticism and for permission to study the Bellevue Hospital group of cases.

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PLEURITIC PAIN: USE OF INTRAVENOUS CALCIUM GLUCONATE IN ITS RELIEF

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It is usually stated in textbooks of medicine and physiology that the pain of pleurisy is due to friction between the inflamed pleural surfaces. This is based partly on the demonstration by Capps and Coleman⁶ that the parietal pleura is sensitive to painful stimuli. Certain clinical observations on relief of pleuritic pain by various methods have indicated, however, that the mechanism of the pain is more complex than simple friction between the pleural surfaces. The purpose of the present report is to describe the relief of acute pleuritic pain by intravenous administration of calcium gluconate, and to discuss the significance of this and other observations in reference to the probable mechanism of the pain.

Method. The procedure consisted of the intravenous injection of 10 to 20 ml. of 10% calcium gluconate solution during a period of 2 to 4 minutes. The effect of this on pleuritic pain will be described in the next section. Two side-effects were noted: a sense of warmth and flushing, and occasional mild nausea. The drug was not used in patients receiving digitalis because of possible toxic reactions.^{3,9} In order to rule out the possibility that the sense of warmth and flushing after calcium played a part in the results obtained, several patients were first given 100 mg. of nicotinic acid intravenously. This caused marked flushing of the skin, but had no effect on the pain.

Results. Thirty patients with acute pleuritic pain due either to pneumonia or pulmonary infarction were treated by injection of calcium gluconate. The results

are summarized in the accompanying table. All but 3 of the patients experienced definite relief of pain. Of the 3 patients

TABLE 1.—RESULTS OF INTRAVENOUS INJECTIONS OF CALCIUM GLUCONATE IN 30 PATIENTS WITH ACUTE PLEURITIC PAIN

Diagnosis	Pneumonia	Pulmonary infarction
Complete relief	4	0
Partial relief	20	3
No relief	1*	2
Total patients	25	5

* This patient obtained no relief of pain with intercostal nerve block.

who were unrelieved, 2 were likewise unaffected by procain block of the intercostal nerves while the third experienced relief from that procedure.

In only 4 of the 27 patients who obtained relief with calcium gluconate did the pain disappear completely and not return. Usually there was a very marked, but not complete relief; this was evidenced by easier, fuller respirations and ability to cough. The effect was evident within 60 seconds after beginning of the injection. The residual pain was described by several patients as a dull aching, unrelated to respiratory movements. When the pain relief was not permanent, there was gradual return after a period of 30 to 60 minutes. Tenderness and hyperalgesia of the chest wall or upper abdominal muscles were also relieved by calcium only to reappear at the same time that the sharp pains on inspiration returned. In 10 patients, a second injection of calcium gluconate was again effective in ameliorat-

ing this pain. Most of the patients in this series were subsequently given more lasting relief by procain block of the intercostal nerves,¹⁷ or by ethyl chloride spray.⁷

The practical value of the use of calcium injection lies in its simplicity. It enables the patient to cough and produce sputum, often of importance in determining the etiology of the pleurisy, and facilitates physical examination of the chest. Furthermore, as stated above, permanent relief of the pain occurs in some instances.

Discussion. In 1940, Buchthal and Clemmesen⁴ reported electromyographic studies on patients with painful muscle spasm. They demonstrated that various drugs, among them calcium salts, brought about relaxation of the muscle spasm, evidenced both by palpable lessening of the spasm and by electromyographic changes. At the same time, pain was relieved. Other reports have emphasized the fact that calcium injection has a definite effect in the restoration of normal muscle tone.^{1,14}

In 1928, Weiss and Davis²¹ obtained relief of pain in pleurisy by injection of procain into the skin at the site of pain and tenderness. Relief was immediate, often complete and permanent. Occasionally, after several hours, the pain returned and a second injection was necessary. They noted in several patients that relief of pain in one area resulted in its appearance at another site. This too could be relieved by intracutaneous injection of procain. They offered the suggestion that normal impulses from the skin play upon a focus in the spinal cord made irritable by increased afferent impulses from the pleura, and these are interpreted as pain.

In 1939, Schnur¹⁸ demonstrated that injection of procain directly into the pleural cavity at the site of maximum pain likewise afforded immediate and sometimes lasting relief.

Price¹⁷ in 1943 reported the use of procain block of the intercostal nerves in pleurisy. He inferred that relief was due to block of the fibers carrying pain, and pointed out that often only one procain block gave permanent relief of pain,

despite the fact that the duration of effect of this drug could not be more than a few hours.

In 1944, Kelly¹² pointed out similarities between chest pain associated with fibromyositis or muscular rheumatism and that accompanying the pleurisy of acute lung infections. Using the method of direct infiltration of the tender intercostal muscles with procain, he was able to obtain relief of pain in both types of disease. He concluded that the rôle played by abnormal sensitivity of the intercostal muscles in pleurisy was an important one perhaps of major significance in the causation of the pain.

Dybdahl⁷ in 1944 described the relief of pleuritic pain by use of an ethyl chloride spray on the skin over the painful area. We also have been able to obtain striking relief with this procedure, many times complete and permanent. While Dybdahl recommended that a series of concentric frozen wheals be made at the site of pain, it has been our experience, as well as that of others employing the spray for other conditions,² that actual freezing of the skin is not necessary. The application of the spray for 20 to 30 seconds, producing only a transient cutaneous anesthesia is often all that is required.

The use of ethyl chloride as a spray for relief of pain was first suggested by Kraus⁸ in 1935 as a rapid treatment of painful distortions of joints. In treating ankle sprains, one application of the spray may give lasting relief, if active motion of the joint is begun immediately and is continued for a time.¹³ Kraus suggested that momentary surface anesthesia in some way abolished painful muscle spasm and that continued active movement so restored the involved muscles to a normal or near normal state that spasm did not recur. Payr¹⁶ in 1934 had described the so-called "chain" effect of painful muscle spasm. The chain consisted of sensory nerve, spinal cord, motor nerve, muscle and sensory nerve. Pain originating anywhere in the course of this chain leads to painful muscle spasm and the pain of the spasm

induces still more spasm and pain as the vicious cycle becomes established. If the chain can be broken at any point, the spasm is relieved and if the muscles can be restored to a more normal state during the pain-free interval (by active movement), the recurrence of spasm can be prevented.

That spasm of striated muscle can serve as primary source of pain was shown by Kabat and Knapp¹¹ who employed erythroidine for the relief of muscle spasm in acute anterior poliomyelitis. As spasm was relieved, pain disappeared. Wolff and his associates^{19,20,22} in their extensive studies on pain mechanisms have demonstrated that certain types of headache are due to spasm of the muscles of the scalp and neck. McClellan and Goodell¹⁵ pointed out the importance of abdominal muscle spasm in pain associated with disease of the urinary tract.

The relief of painful muscle spasm by curare has been demonstrated repeatedly.¹⁰ This drug seems to have a selective action on hypertonic muscles, relieving spasticity with little effect on muscles of normal tone.⁵ We have had occasion to use curare

in 2 patients suffering from severe pleuritic pain due to lobar pneumonia and in both of them the pain was alleviated by this treatment.

The foregoing observations together with our results with intravenous calcium gluconate seem to indicate that a major portion of the pain associated with pleuritis is due to a painful spasm of the intercostal muscles which perpetuates itself in a vicious cycle of spasm, pain, and more spasm. Relief by any method seems to depend upon interruption of this cycle at some point.

Summary. Acute pleuritic pain was relieved in 27 of 30 patients by intravenous injection of calcium gluconate. This furnishes additional evidence that much of the pain of pleurisy is due to spasm of the intercostal muscles.

A "chain-theory" of painful muscle spasm as postulated by Payr would explain satisfactorily the relief of pleuritic pain by such varying methods as intracutaneous, intramuscular, and intrapleural injection of procain, intercostal nerve block, ethyl chloride spray, curare or intravenous calcium gluconate.

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CENTRAL NERVOUS SYSTEM INVOLVEMENT DURING MUMPS

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THERE is abundant evidence that central nervous system involvement occurs frequently during infection with the virus of mumps.²⁹ That it may be a constant feature of this infection is not unlikely. It has been observed to precede, accompany or follow salivary gland swelling, and sometimes to present the only manifestation of mumps infection.^{2,5,15,23,25} In most cases of mumps, symptoms of meningo-encephalitis do not occur or are mild. The frequency with which it has been recognized clinically has varied widely.²⁹ However, examination of the spinal fluid during mumps has revealed abnormalities in a significant proportion of each series of cases in which routine lumbar punctures were made.^{4,9,12,23,28} Experience would seem to indicate that involvement of the central nervous system during mumps is of little significance in the great majority of cases. Nevertheless, severe nervous system damage has been observed to occur.

It is the purpose of this report to present the manifestations of central nervous system involvement which were observed during the course of mumps in 77 consecutive cases in which lumbar punctures were done. The results of the study of 28 of these patients have been previously reported in brief.¹⁴ A patient is described in whom disabling residual nervous system symptoms persisted.

Methods. Clinical observations and spinal fluid examinations were made on 77 con-

secutive cases of mumps which were observed in a U. S. Army General Hospital in England during the period November, 1942 to April, 1944. Most of the patients were young American soldiers. Thirteen were American civilians, the oldest of whom was 45. All were men. The diagnosis of mumps was supported by the presence of parotitis in all but one patient; he had epididymo-orchitis. In those without symptoms of meningoencephalitis, an initial lumbar puncture was usually done between the 8th and 12th day of illness. This time was chosen because it was believed that abnormalities were most likely to be discovered at this mid-period in the disease.^{20,25,29} If clinical evidence suggestive of central nervous system involvement appeared, lumbar puncture was performed at that time. Patients whose spinal fluid was abnormal had subsequent lumbar punctures at 10-day intervals, in most cases, until the abnormality disappeared. Examination of spinal fluid was performed immediately after withdrawal. This included a total and differential cell count, qualitative test for increased globulin content by the method of Pandy and quantitative estimation of sugar and chlorides. Quantitative protein determinations were made on the fluid of 45 cases. The generally recognized normal range was used in evaluating the content of sugar, chlorides, and protein. Evidence of central nervous system involvement was not considered established unless a pleocytosis of 10 or more leukocytes per cu. mm. of spinal fluid was present.

Results. A summary of the incidence of central nervous system involvement

during mumps in this series is presented in Table 1. Certain pertinent findings in the 26 cases who had an increase in the number of leukocytes in the spinal fluid are tabu-

TABLE 1.—SUMMARY OF INCIDENCE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN 77 CASES OF MUMPS*

Total number of patients	77
Number who had pleocytosis in spinal fluid	26(33.7%)
Cases with clinical evidence of meningoencephalitis	9(11.7%)
Number with pleocytosis in spinal fluid	8
Cases with no clinical evidence of meningoencephalitis	68
Number with pleocytosis in spinal fluid	18
Proportion of patients without signs who had pleocytosis	26.4%
Number of patients in whom epididymo-orchitis occurred	19(24.7%)
Number in this group whose spinal fluid showed pleocytosis	8
Proportion with epididymo-orchitis who had pleocytosis	42.1%
Number of patients with residual central nervous system sequelæ	1

* Pleocytosis (10 or more leukocytes per c.mm. of spinal fluid) was arbitrarily regarded as the requirement for evidence of central nervous system involvement.

lated in Table 2. Nine (11.7%) of the total of 77 patients had symptoms suggestive of meningoencephalitis and 8 of these showed pleocytosis in the spinal fluid. The other 68 patients had no clinical evidence of meningoencephalitis, but 18 (26.4%) of them had increased spinal fluid cell counts.

Pleocytosis in the spinal fluid occurred more frequently in patients who also developed epididymo-orchitis, 8 or 42.1% of 19 cases. There was no correlation between the number of cells and clinical evidence of central nervous system involvement.

CASE 26 G.P. AGE 26

ONSET BILATERAL PAROTITIS 24 MAY 1943
ONSET HEADACHE MILD STIFF NECK 27 MAY 1943

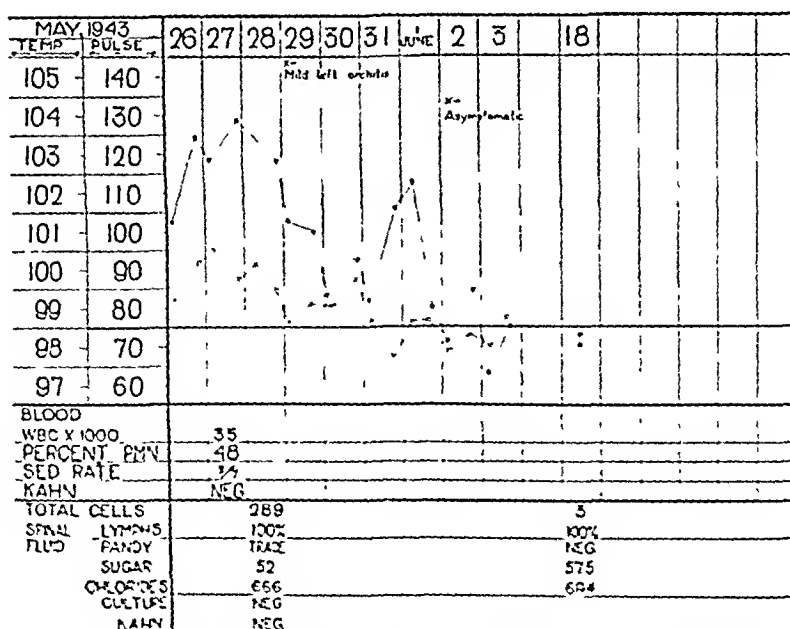


FIG. 1.—The course of a patient with mild symptoms of meningoencephalitis and pleocytosis in spinal fluid.

TABLE 2.—SUMMARY OF 26 PATIENTS WITH EVIDENCE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT DURING MUMPS*

		Manifestations of mumps					Central nervous system manifestations																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
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* Only cases with 10 or more leukocytes per c.mm. of spinal fluid are listed.

The chloride and sugar content of the spinal fluid was normal in all patients and showed no significant change when other abnormalities were present. In the 45 patients in which total protein was measured, it was over 50 mg. per 100 cc.

in only 4 of the 11 who also had pleocytosis. There was no correlation between the level obtained and the degree of pleocytosis. The spinal fluid of 9 other patients had amounts of protein over 50 mg. per 100 cc. without increase in total leukocytes or

increases the incidence to 35 (45.5%) of a total of 77 examined.

The clinical evidence of meningoencephalitis observed in 9 cases included headache, stiff neck, nausea, vomiting and vertigo, one or more in varying degree in each patient. Except for 1 patient, to be described, the symptoms were mild and cleared rapidly. Relief of headache and nausea occurred after lumbar puncture in nearly every instance. No significant neurological signs were observed. Figures 1, 2, and 3 present the clinical course and the findings in 3 patients. The case represented in Figure 1 had bilateral parotitis followed by mild stiff neck and headache, and the spinal fluid was abnormal. The one represented by Figure 2 had similar symptoms and signs, but with more severe headache, stiff neck, and nausea. Fever and other symptoms disappeared rapidly after lumbar puncture. The patient in Figure 3 had mild unilateral parotitis, mild constitutional reaction and no symptoms referable to the central nervous system. His spinal fluid contained the greatest number of cells.

The data on patients with pleocytosis in the spinal fluid are listed in Table 2. In general, the degree of pleocytosis diminished rapidly within a few days but this was variable. The number of days in hospital for each patient is indicated. The duration of hospitalization was dependent upon the disappearance of abnormalities in the spinal fluid. Symptoms disappeared early. The patients were kept at nearly complete bed rest while abnormalities were present. It seemed reasonable to regard these changes, even though slight, as evidence of the presence of diffuse central nervous system involvement. The patients in whom the spinal fluid was normal were permitted activity when clinical signs of mumps had subsided and were discharged on the 20-21st day, in keeping with the policy of quarantine.

One patient of the series has remained seriously disabled following acute meningoencephalitis. His course will be described in some detail.

Case Report. The patient, a 24 year old white male, was well until October 3, 1943. On this day he developed mild sore throat and fever which was thought to be due to pharyngitis, endemic in the region at the time. The fever continued and he was admitted to the hospital on October 5. On this day the temperature rose to 105° F., the next day to 106° F. and the patient became irrational. Swelling of both testes was noted on this day. Examination revealed the patient to be flushed and irrational. He lay on his side, knees drawn up, head slightly retracted and neck moderately stiff. The pharynx was slightly reddened. The fundi and external ocular movements appeared normal. There was no enlargement of the salivary glands. Both testes were very tender and twice normal in size. The abdominal reflexes were equal and active. The right patellar jerk was diminished and the right ankle jerk was absent. There was an abnormal plantar response, not a typical Babinski sign, on the right. The total leukocyte count in the blood was 16,800 per cu. mm.; P.M.N. 68%, lymphocytes 20%, monocytes 10%. Urinalysis was normal. The spinal fluid revealed: 170 leukocytes per cu. mm., 80% lymphocytes; total protein: 30 mg. per 100 cc.; Pandy test: trace, chlorides 659 mg. per 100 cc.; Gold curve: 0001110000. Blood and spinal fluid Kahn tests were negative. The initial impression was acute epididymo-orchitis and meningoencephalitis due to mumps. During the next 4 days the temperature gradually became normal and remained so. The patient slowly became rational. After 2 weeks the mental confusion had improved but was still present. Swelling of the testes disappeared in 1 week. By October 24 he was cooperative but slightly confused, euphoric but with lability of mood. Occasional uncontrollable tremor occurred of the right arm and head, especially when upset. His voice was harsh and hard to understand. Visualization of the larynx revealed general atony with incomplete paresis of the adductor muscles. The gag reflex was absent. There was difficulty in reading fine print, vision 20/60 J4 in both eyes. Pupils were equal and reacted normally. Hearing was normal. There was marked ataxia with mild asterognosis and adiadochokinesia. The left patellar reflex was slightly more active than the right. Other reflexes, including abdominal and

cremasteric, were equal and active. General muscle power was diminished symmetrically. The testes appeared normal.

After 2 months the patient's judgment became more acute and euphoria diminished to be replaced by occasional episodes of depression. Speech was clearer and tremor of the right arm and head had disappeared. He was able to stand and take a few steps unaided, but ataxia remained marked. Vertigo was present on standing. Vision was not improved, the gag reflex remained absent and atony of the larynx persisted. Deep and superficial reflexes were equal and active. The right plantar response remained abnormal but did not represent a typical Babinski sign.

The total and differential blood count was normal on October 26 and subsequently. There was no anemia. Spinal fluid examination of October 26 revealed 24 cells, 75% of which were lymphocytes; total protein, 45 mg. per 100 cc., Pandy test negative; sugar, 66 mg. per 100 cc., chlorides, 698 mg.; Gold curve, 0000000000. The spinal fluid on November 13 was normal.

The family and past history was non-contributory. He had not previously had mumps. One contact developed typical mumps 2 weeks after onset of this patient's acute illness.

The patient was seen last on January 1, 1944. At that time his condition was as described above. In a letter, received in April, 1947, the patient indicated that improvement had taken place slowly in the 3-year interval, but that considerable residual disability remained.

In summary, this patient suffered from acute meningoencephalitis which occurred during the course of bilateral acute epididymo-orchitis, which was probably due to mumps. Specific antibody studies were not made. The possibility that the encephalitis was caused by an unknown intercurrent virus cannot be eliminated. Manifestations of severe central nervous system damage, with slight tendency to improvement, have persisted for at least $3\frac{1}{2}$ years since the acute episode. This case is presented in some detail because of the likelihood that mumps was the cause of the serious central nervous system damage which resulted.

Discussion. Many studies have demonstrated that meningoencephalitis is a feature of mumps.^{4,9,12,17,20,23,25,27,28} The present report supplies an additional series of patients in which clinical and spinal fluid examinations indicated the presence of central nervous system involvement in a significant proportion. It seems reasonable to believe that every patient with mumps is subject to the neurotropic effects of this virus. The frequency and character of the manifestations of this involvement must depend upon unknown individual factors. Enders and his colleagues have developed serologic and intradermal tests which have made possible specific diagnosis of infection with the virus of mumps.⁸ The use of these methods has demonstrated that acute aseptic meningoencephalitis is frequently due to this specific agent.^{8,13,24}

The clinical significance of the neurotropic activity of the mumps virus is not clear. In the great majority of cases of mumps only minor manifestations of encephalitis have been discovered. These cases are not followed by demonstrable central nervous system injury. However, severe encephalitis with residual disability due to nervous system damage sometimes occurs. Cases of this kind are unusual but numerous instances are on record.^{6,7,11,16,17,18,20} Fatalities have been recorded. In a review of the literature Donohue found 10 cases in which histologic studies of the nervous system had been made; 7 of these were considered doubtful or inadequately studied.⁷ He reported one additional case. The morphologic changes in the remaining 4 cases were variable but resembled those associated with post-infection encephalitis following many diseases. The view that severe encephalitis which sometimes develops during mumps is due to the activation of an unknown latent virus is widely expressed.^{7,20,21,29} This is a reasonable hypothesis but is based upon circumstantial evidence. Globus,¹⁰ after a comprehensive study concludes: "By placing side by side the various forms of inflammatory diseases of the central nervous system, a striking confluency of all the encephalitis

forms has been revealed, and it has been suggested that the minor histological differences express mainly the degree rather than the character of the pathologic process, and it is not unlikely that we are dealing here with variations in intensity of the excitant and variations in local vulnerability of the tissue rather than with the distinct types of causative agents." In recent years, studies of encephalitis due to different specific viruses have demonstrated that morphologic changes are variable. Since the mumps virus exhibits a definite neurotropic tendency it seems reasonable to suspect that it may occasionally be the primary specific cause of severe encephalitis. The sequence of events in the case reported in this paper suggested that all of the manifestations were due to the same agent. The question of the cause of encephalitis which occurs during many infections, including mumps, remains unsettled. The use of techniques now available will help to clarify the problem. In the management of patients it would appear sensible to regard any manifestation of encephalitis during mumps with some concern.

Many infections may be accompanied rarely by severe central nervous system involvement.^{3,10,19,21,22,26,30} This is usually classified as post-infectious encephalitis. However, manifestations do not always follow the primary disease but sometimes make their appearance beforehand.¹ Of the exanthemata, measles is most frequently complicated by encephalitis.

There is a growing realization that invasion of the central nervous system, without clinical evidence of this involve-

ment, may be a regular feature of many infections. For this reason the spinal fluid of 6 consecutive adult patients with measles was examined at the same time and under the same conditions as those in the study of mumps. Lumbar punctures were made between the 6th and 12th day of the disease. The spinal fluid cell counts were as follows: 26, 14, 11, 2, 1 and 0 cells/cu. mm. The patient whose spinal fluid contained 26 cells/cu. mm. had nausea, vomiting, slight confusion and mild stiff neck. The other patients had no clinical evidence of central nervous system involvement.

Study of the spinal fluid during infections is the simplest available means of investigating the presence of central nervous system involvement. The information obtained is limited but helpful. Studies similar to those reported are needed to determine the importance of the neurotropic effects of many infections.

Summary. The incidence and characteristics of central nervous system involvement was studied in 77 consecutive cases of mumps in which spinal fluid examinations were made. Pleocytosis (10 or more cells per cu. mm.) was present in the spinal fluid of 26 (33.7%). Clinical manifestations of meningoencephalitis were recognized in 9 cases. These were mild in all but 1 patient. The course of this patient is described. He suffered disabling residual nervous system damage which has persisted for 3½ years. The problem of encephalitis which occasionally accompanies infectious diseases is briefly considered.

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HORMONAL HYPERTENSION AND NEPHROSCLEROSIS AS INFLUENCED BY THE DIET*

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It is now a firmly established fact that the treatment of rats with lyophilized anterior-pituitary (LAP) leads, under certain experimental conditions, to characteristic renal and cardiovascular lesions^{12,13,14,16} which are similar to those produced by desoxycorticosterone acetate (DCA) or various chronic non-specific stresses. The histologic changes have been previously described:^{11,15} the renal lesions are mainly characterized by enlargement and hyalinization of the glomeruli, formation of hyaline casts, dilatation of the renal tubules and thickening and hyaline necrosis of arteriolar walls. These pathologic modifications are considered to be similar to those described in the malignant type of arterial hypertension. This condition will be referred to as *nephrosclerosis*.

Previous work shows that a marked hypertension is part of the syndrome produced by DCA overdosage or chronic non-specific stress.^{11,15} Therefore we felt it important to determine whether the LAP nephrosclerosis would also be accompanied by elevation of the blood pressure. Furthermore, since it is known that a high protein diet is indispensable for the development of LAP nephrosclerosis,⁶ we considered it pertinent to investigate whether it would also be essential for the production of hypertension. Secondly, as it has been found that rats receiving a

diet deficient in the heat-stable fraction of the vitamin-B complex develop an increased blood pressure^{2,3} and that the kidney lesions produced solely by high protein diets may be favorably influenced by addition of vitamins to the ration (see 3 for the pertinent literature), we also studied the possible protective effect of a few vitamins of the B-complex against the LAP nephrosclerosis and hypertension.

In the work described below we shall attempt to show that the LAP-nephrosclerosis is accompanied by hypertension, and that a low casein diet is effective both in preventing the histological lesions and the elevation of the blood pressure. We also present some evidence showing that an excessive amount of choline chloride tends to diminish the observed hypertension.

Methods. Nephrosclerosis was produced by a method previously published.⁷ The procedure consists in the subcutaneous administration twice daily, of 10 to 15 mg. of lyophilized anterior-pituitary, to unilaterally nephrectomized castrated male rats (B.W. 40-80 gm.). If the animals are simultaneously given a 30%-casein, high-NaCl diet⁸ beginning nephrosclerosis is obtained at the end of 21 days in almost all the rats.

The blood pressure was estimated by the direct method; a small needle washed in heparin, and connected with an open mercury manometer, was inserted into one

* A verbal preliminary account reporting on part of this work appeared in *Federation Proc.*, 6, 182, 1947.

of the carotid arteries and the pressure read as soon as the mercury level became constant. The determination was always performed under ether anesthesia. In order to avoid undue bleeding of the animal, the mercury level in the manometer was pre-

viously elevated to the expected value of the blood pressure.

The basic partially synthetic diets used throughout this investigation have already been described in detail⁶ and had the following composition (Table 1):

TABLE 1.—COMPOSITION OF TWO BASIC SYNTHETIC DIETS (PARTS, PER CENT)

	Diet 1	Diet 2	Supplements	
Casein	30	15	1. Thiamine chloride	0.8 mg./100 gm. diet
Corn starch	59	74	2. Riboflavin	0.8 mg./100 gm. diet
Fat	1	1	3. Pyridoxine	0.8 mg./100 gm. diet
Cod liver oil	1	1	4. Ca pantothenate	4.0 mg./100 gm. diet
Bulk	1	1	5. Nicotinic acid	1.0 mg./100 gm. diet
Sodium chloride	4	4	6. Choline chloride	100.0 mg./100 gm. diet
Mineral mixture	4	4	7. Tocopherol acetate	10.0 mg./rat/weekly

The major difference between the 2 diets consists in a decrease of the casein content from 30% in Diet 1, to 15% in Diet 2. The corresponding increase in the carbohydrate percentage in Diet 2, has been shown not to exert any influence upon the incidence and severity of nephrosclerosis.⁶ Except for the high proportion of sodium chloride, which is well tolerated, these 2 diets are fairly close to optimal.

The B-vitamins were supplied in the amounts indicated in Table 1; we will subsequently refer to such concentrations as the "normal amount" of vitamins. When we say, for example, that 10 times the normal amount of choline chloride was added to the diet, we mean that instead of the 100 mg. of choline chloride per 100 gm. of diet, 1000 mg. per 100 gm. of ration were used. The same applies to the other factors studied.

Experiments and Results. DIETARY PROTEIN AND HYPERTENSION. Two groups of 10 castrated male unilaterally nephrectomized, black and white rats, whose body weight ranged between 45 to 60 gm., were given a 30% casein diet (Diet 1). Group 1 received 20 mg. of LAP, suspended in 10% alcohol, in 2 daily subcutaneous injections, during 3 weeks. Group 2, acted as control and received no LAP. Two other similar groups of rats (Groups 3 and 4), were treated as Groups 1 and 2 respectively, but were fed a 15% casein diet (Diet 2) during the experimental period. At the end of 21 days the blood pressure was determined, and the animals were autopsied. The incidence and severity of the nephrosclerosis was

TABLE 2.—EFFECT OF THE CASEIN CONTENT OF THE DIET ON THE HYPERTENSION PRODUCED BY LAP* (AVERAGES AND STANDARD ERRORS)†

Groups	No. rats	Diets‡	Dose of LAP (mg./daily)	Final body wt.	Adrenal weight (mg.)	Kidney wt. mg./100 cm of body surface	Nephrosclerosis		Blood pressure	
							Incidence (%)	Severity (%)	(mm Hg§)	Percentage of hypertensive animals
1	19	30% Casein	..	126 ± 3.0	28.3 ± 0.7	455 ± 10	0	0	123 ± 1.8 (18)	0
2	36	30% Casein	20	163 ± 3.0	64.2 ± 1.6	855 ± 49	85	63	145.4 ± 7.5 (24)	65
3	17	15% Casein	.	114 ± 3.2	25.0 ± 1.3	379 ± 12	0	0	113 ± 1.6	0
4	27	15% Casein	20	154 ± 3.6	41.9 ± 1.3	491 ± 51	11	11	105 ± 4.1 (14)	0

* Labeled anterior pituitary.

† The standard errors cited in this and subsequent Tables were calculated by the equation:

$$\text{S.E.M.} = \sqrt{\frac{\sum d^2}{n(n-1)}} \quad \sqrt{\frac{\sum d^2}{n(n-1)}}$$

‡ Diets 1 and 2.

§ Figures in parentheses refer to number of determinations.

¶ Hypertensive average 157 ± 4 mm. Hg.

calculated as previously described.⁷ The weight of the adrenals and kidneys was determined after fixation in "Suza" mixture for 24 hours. Subsequently the renal lesions were also histologically evaluated, and expressed as a percentage of the maximum possible.

The first experiment was repeated 4 times, but in the last 2 instances, the groups not receiving LAP were omitted. As the results were essentially the same, they are summarized conjointly in Table 2. The number of rats refers to those surviving at the end of the experiments.

Table 2 confirms the previously observed fact,⁶ that the composition of the diet is an essential factor for the production of nephrosclerosis by anterior-pituitary overdosage. While in the 15% casein group the incidence and severity of the renal lesions was very low, in the 30% casein group the incidence was 88% and the severity of the nephrosclerosis, 63%. In the control groups, not treated with LAP, the kidneys were entirely normal. Moreover, according to our expectation, the blood pressure in the 30%, LAP treated rats, was far above the normal average* and the rise statistically significant ($P = < 0.01$). The value 145 ± 4 (standard error) mm. Hg is not, however, a true figure because it is composed of 16 hypertensive plus 8 normotensive rats. The hypertensive average (average of the 16 blood pressures higher than 135 mm. Hg) is 157 ± 4 mm. Hg which indicates, beyond any doubt, that the LAP nephrosclerosis is accompanied by a pronounced degree of hypertension. In this connection it is, however, indispensable to recall two facts: first, the direct method gives only the mean pressure which is much lower than the systolic; second, the observed elevation of the blood pressure was induced in a rather short period of time.

The second striking fact observed was that among the LAP-treated rats, those on 30% casein revealed a rather high

incidence of hypertension while in the 15% casein group the blood pressure remained low.

In our opinion these observations conclusively demonstrate that below a minimum protein content (about 15%) LAP hypertension and nephrosclerosis cannot be obtained, at least under our experimental conditions.

Unexpectedly the comparison of the average blood pressure within the control groups, one receiving the 15% casein and the other the 30% protein ration, also reveals a statistically significant difference between both. Subsequently we proved that this difference had been due to the unilateral nephrectomy; intact animals treated with the same diets failed to present any difference between their blood pressures.

The differences in kidney and adrenal weights confirm our previous findings.⁶ However, we want to emphasize the considerable difference in adrenal weight between Groups 2 and 4. It is statistically significant when calculated either in absolute terms or as a function of body weight. We believe that the parallelism between this pronounced adrenal enlargement and hormonal hypertension, is particularly noteworthy.

Regarding the effect of diet alone on suprarenal weight, we wish to emphasize that in rats fed a 15% protein ration the adrenal weight was 25.0 ± 1.3 (standard error) mg.; on the other hand, in the animals given a 30% casein diet the adrenal weight was 28.3 ± 0.7 (standard error) mg. The significance of this difference is dubious and if the adrenal weights are calculated as mg. per 100 gm. of body weight, the difference is not significant.

RELATION OF THE B-VITAMINS, TO HYPERTENSION AND NEPHROSCLEROSIS. In order to evaluate the possible rôle of the B-vitamins in our experimental hypertension and nephrosclerosis we first investigated the effect of the addition to the

* The mean blood pressure in the control rats receiving Diet 1 was 123 ± 7 (standard deviation) mm. Hg; therefore, a blood pressure of 123 ± 14 mm. Hg (20) should include 95% of the normal distribution, hence we felt justified in regarding 135 mm. Hg as the approximate highest limit of normal pressure.

diet of 10 times the "normal" amount of the B-vitamin mixture employed. As a small beneficial effect could be observed in this preliminary experiment, we repeated it twice more and in subsequent work we decided to find out if the protective effect would have been due to the vitamin mixture as a whole or to an individual factor only. To elucidate this point we planned some experiments in which the 30% casein diet was supplemented with 10 times the "normal" amount of each factor individually in addition to the "normal" amount of the whole vitamin mixture. As among the 6 B-vitamins so investigated only choline chloride† seemed to be beneficial, this observation was also repeated 2 more

times. Each group of rats consisted of 10 animals treated exactly as in the experiments previously described; with the difference that the diet was supplemented as indicated in Table 3. In this table only the groups which were fed the diets containing 10 times the "normal" amount of all the vitamins and the ones containing 10 times the "normal" amount of choline chloride are tabulated. The results pertinent to the other 5 vitamins (thiamine, riboflavin, pyridoxine, calcium pantothenate, and nicotinic acid) are not listed because they were essentially negative. The groups treated with 30% casein but with "normal" vitamin supplements, are included in Table 3, for comparative purposes. Table 3 shows that the addition

TABLE 3.—EFFECT OF THE VITAMIN CONTENT OF THE DIET ON THE HYPERTENSION PRODUCED BY LAP*
(AVERAGES AND STANDARD ERRORS)

Groups	No. rats	Diet†	Dose of LAP (mg./daily)	Final body weight	Adrenal weight (mg.)	Kidney wt. mg./100 cm. of body surface	Nephrosclerosis		Blood pressure	
							Incidence (%)	Severity (%)	(mm. Hg‡)	Percentage of hypertensive animals
1 . . .	27	30% Casein 10 × Vits.	20	156 ± 3 0	59 3 ± 1 8	900 ± 47	85	57	130 ± 3 (12)	33
2 . . .	36	30% Casein	20	163 ± 3 0	64 2 ± 1 6	858 ± 49	83	63	145 ± 4 (24)	66
3 . . .	27	30% Casein 10 × Choline chloride	20	163 ± 3 2	59 0 ± 1.7	731 ± 25	75	33	126 ± 2 (26)	15

* Lyophilized anterior pituitary.
† Diets 1 and 2 plus indicated supplementation.
‡ Figures in parentheses represent number of determinations.
§ Hypertensive average 157 ± 4 mm. Hg.

of 10 times the normal amount of the vitamin mixture or of choline chloride to the diet produced a significant decrease in the hypertension. We do not attach much importance to this observation, however, because the amelioration of the kidney lesions was practically none. We believe that more work has to be performed before concluding that choline chloride is effective in this type of hormonal hypertension and nephrosclerosis.

Discussion. For the reasons outlined in the introduction of this paper, the observed concomitant development of

LAP-nephrosclerosis with high blood pressure was to be expected and, in our opinion, it represents further evidence that the anterior pituitary hormones may play a rôle in the pathogenesis of arterial hypertension. This laboratory has repeatedly defended the idea that non-specific stress, acting on the anterior lobe of the hypophysis through an unknown mechanism may be one of the stimuli which ultimately lead to a malignant type of hypertension. This aspect of the question has been recently reviewed in detail, emphasizing the central position of the hypophysis in the pathogenesis of arterial

† The classification of choline chloride among the B-vitamins has been judiciously criticized by E. W. McHenry and J. M. Patterson: *Physiol. Rev.*, 24, 128-167, 1944.

hypertension in particular and of the "diseases of adaptation" in general.^{14,16}

On the other hand, the part played by the adrenal glands in the pathogenesis of LAP-nephrosclerosis has been firmly established, since this condition cannot be obtained in adrenalectomized animals.⁵

The results presented in this communication point to the diet as one important factor in the genesis of this type of hypertension but we feel that its contribution is rather secondary as compared to the importance of the hypophyseal-adrenal system. In fact, we are particularly impressed by the observation that in the high protein groups the adrenals were markedly enlarged when compared with the corresponding glands of the low protein groups. It is probable that the diet merely accentuates the corticotrophic action of LAP or increases endogenous mineralocorticoid production to the hypertension-producing threshold, although available data does not permit one to favor any one of these assumptions.

Experiments now under way show that the hypertension produced by DCA is not influenced by the diet in the same drastic manner as the LAP hypertension; animals receiving large doses of DCA develop nephrosclerosis and hypertension of almost equal intensity on diets containing 15% or 30% casein. This seems to indicate that the part played by the high-protein diet in the LAP hypertension is predominantly, as we previously stated, to permit a pronounced enlargement of the suprarenal gland.

The effect of dietary protein alone on adrenal weight has been investigated by different investigators. While Tepperman, Engel and Long¹⁷ claimed to have found an increase in adrenal weight on a high protein ration, Benua and Howard¹ and Ingle, Ginther and Nezamis⁸ described negative findings and Leatham⁹ first obtained no change and subsequently,¹⁰ a barely significant increase. Our own results are also inconclusive except under

LAP treatment, when the difference was always striking.

We do not believe that the results obtained with choline chloride indicate any relationship between our condition and the kidney lesions produced by choline deficiency. It has been established that 1 to 2 mg. per day of choline chloride prevents the hemorrhagic kidney⁴ and even should a higher level of metabolism (induced in our rats by LAP treatment) increase choline requirements, the amount of choline chloride in our regular diet (100 mg. per 100 gm. of food) appears amply sufficient.

Summary. In the present paper the authors present a series of experiments, on the nephrosclerosis produced after anterior pituitary overdosage. The work deals particularly with the effect of diet (protein and B vitamin contents) upon the hypertension which accompanies this experimental condition. From the results the following conclusions were derived:

1. The LAP-nephrosclerosis was concomitant with a pronounced degree of hypertension in a high percentage of the animals, the hypertensive average being 157 ± 4 mm. Hg (standard error).

2. The hypertension produced by LAP treatment on a 30% protein ration was prevented by decreasing the casein concentration to 15%.

3. Five vitamins of the B group, namely, thiamine, riboflavin, pyridoxine, and calcium pantothenate, were inactive against the hypertension and nephrosclerosis but choline chloride had a slight beneficial effect if given in excessive amounts (1 gm. per 100 gm. food).

4. A very pronounced adrenal enlargement was always present in the hypertensive rats.

5. There was no statistically significant difference in adrenal weight between animals receiving a 15- or a 30%-casein diet. The difference was, however, highly significant if, in addition to the ration, the animals were simultaneously treated with large amounts of anterior pituitary.

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THE MANAGEMENT OF TETANUS WITH CURARE: REPORT OF TWO CASES

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DEATH from tetanus may result from spasm of the respiratory muscles, toxemia, pulmonary complications secondary to oversedation, or the cumulative effects of exhaustion, dehydration and inadequate nutrition. Tetanic contractions contribute importantly to the manifestations of the disease and, in the past, they have been treated usually by heavy sedation. The use of large amounts of sedatives is associated with a high incidence of pulmonary complications. Moreover, sedatives often fail to control adequately tetanic seizures. Curare, by blocking the transmission of the nerve impulse at the myoneural junction, reduces muscle spasm and results in marked muscular relaxation. Thus, it should be a valuable adjunct in the management of tetanic contractions. As long ago as 1894 Hoche⁴ employed curare in the treatment of tetanus. More recently Cole,¹ Mitchell,⁵ and West⁶ have used either the crude drug or its chief active principle, curarine. However, in the past curare was not extensively employed in treating tetanus because the available preparations varied greatly in potency and the response to a given dose was unpredictable. In 1943 Cullen and Quion,² using a highly purified preparation of curare, satisfactorily controlled tetanic seizures in one patient. Pure preparations, standardized by biological assay, are now commercially available. The following case reports demonstrate the value of curare in the management of tetanus and illustrate a dangerous complication induced by it in one instance.

Case Reports. CASE 1. A 40 year old laborer was admitted to Vanderbilt University Hospital, January 7, 1947, complaining of stiffness of the jaws and neck; 15 days previously he had crushed his right finger between two railroad ties. Tetanus antitoxin was refused because on several previous occasions nausea, chills and fever had followed its administration. The wound became infected locally without lymphangitis or constitutional symptoms. He felt well until 3 days before admission when he awoke with slight stiffness of the neck and jaws. There developed gradually increased muscular irritability. Sudden noises or jarring caused generalized painful muscular contractions. These symptoms steadily increased in severity. Eighteen hours before admission he became unable to urinate.

The past history was not remarkable except that in August, 1945, and on several previous occasions, he had received tetanus antitoxin following a minor injury.

Physical examination revealed a well-developed and nourished man who was in moderate discomfort. The neck was stiff and trismus prevented opening of the mouth more than 1 or 2 cm. There was generalized muscular hyperirritability. Slight jarring of the bed caused painful muscular spasms and dyspnea. The tip of the right ring finger was lacerated and pus was exuding from beneath the nail. The heart and lungs were normal. The abdomen was tense and the rectus muscles were spastic. All of the tendon reflexes were hyperactive.

The white blood cell count was 19,000/cu. mm. with 73% segmented forms.

Hospital course: Following a negative intradermal skin test for hypersensitiveness to horse serum, the patient was given 45,000

* Intocostin is a curare preparation, standardized by biological assay, containing 20 units per cc.

units of tetanus antitoxin intramuscularly. Under sodium pentothal anesthesia the necrotic skin and the medial portion of the nail of the infected finger were cut away. *Clostridium tetani* was cultured from the débrided tissue. A filtrate of the culture of this organism produced convulsions in mice.

During the first 3 hospital days the patient remained moderately ill. The rectal temperature rose to 101.8° F. daily and there were frequent painful generalized muscular spasms accompanied by slight dyspnea. Catheterization of the bladder was necessary because of urinary retention.

The first injection of 60 units of intocostarin* was given on the morning of admission. It was followed immediately by marked subjective improvement and moderate muscular relaxation. Hyperirritability gradually returned and a second dose of 20 units was given after 1½ hours. A total of 9 intravenous injections of intocostarin,* ranging between 20 and 60 units each and averaging 40 units each, were given during the first 4 hospital days. Sodium phenobarbital was administered at frequent intervals and he received several injections of codeine for the painful muscular contractions. Penicillin in doses of 30,000 units at intervals of 3 hours was administered for 17 days. The doses of curare which were employed in this case were not sufficient to control the muscular contractions completely throughout each 24 hour period. Nevertheless, the results obtained indicated conclusively that curare caused muscular relaxation and alleviated the painful spasms and that it was more effective than codeine in controlling pain. The subjective relief provided by it was more impressive than were the objective signs of improvement.

The patient made an uneventful recovery and was discharged 19 days after admission to the hospital.

CASE 2. A 38 year old caretaker was admitted to Vanderbilt University Hospital on February 23, 1947. On February 16 he noted stiffness of the neck and jaws, slight trismus and headache. He remained ambulatory until the day before admission when he experienced dysphagia, inability to open his mouth, generalized muscular stiffness and dyspnea. He had several painful tetanic seizures. There was no history of injury. He had never received tetanus toxoid or antitoxin.

The past history was non-contributory.

He was acutely ill and sweating profusely. Cyanosis was marked. The temperature was 100° and tachycardia was present. There was evidence of dehydration. There was marked opisthotonus, trismus, nuchal rigidity and generalized muscular rigidity. The characteristic sardonic facies was present. Speech was not impaired. The respirations were labored and stridulous although movement of the thoracic cage was almost imperceptible. The abdomen was board-like and the lumbar muscles were in a completely rigid state. The jaws could be opened only ½ cm. All of the deep reflexes were hyperactive. Over the knuckle of the right index finger there was a superficial abrasion 1 cm. in length which was covered by a dry crust.

The white cell count was 16,500, of which 86% were neutrophils. Lumbar puncture revealed normal cerebrospinal fluid. Cultures from the abrasion on the finger did not yield *Clostridium tetani*.

Hospital course: From the outset it was apparent that laryngeal spasm was severe and a factor in the production of the marked dyspnea and cyanosis. Within a 4 hour period, 140 units of intocostarin were given intravenously in divided doses. After sufficient intocostarin had been given to overcome the laryngeal and generalized muscle spasm, it became necessary to hold the tongue forward. Otherwise, it fell back in the mouth and occluded the glottis. However, respiratory paralysis did not occur. At intervals oxygen was administered by mask. Initially, the accumulation of secretions in the pharynx proved troublesome. Atropine appeared to be helpful in its suppression.

The patient exhibited negative skin reactions to horse serum and 40,000 units of tetanus antitoxin were administered intramuscularly. Penicillin in doses of 30,000 units intramuscularly every 3 hours was also given. Intocostarin was employed in doses of 40 units intramuscularly at 4 hour intervals with complete control of muscle spasms and trismus. Sodium phenobarbital 0.24 gm. daily, was administered. He was kept fairly comfortable on this therapeutic régime and was able to take food by mouth and to void and defecate normally.

The patient slowly recovered. He was given 10,000 units of tetanus antitoxin daily for 4 days, during which time the temperature remained slightly elevated. Penicillin

was discontinued on the 9th hospital day. Our supply of intocostin became exhausted on the 9th day of treatment and for 16 hours none was administered. During this period nuchal rigidity and trismus reappeared and there were several mild muscular spasms. With the reinstitution of curare treatment these symptoms promptly subsided. Intocostin was discontinued on the 18th hospital day. The patient was then able to sit beside the bed and in a day or so became ambulatory on the ward. He had completely recovered when discharged from the hospital 34 days after the onset of the illness.

Comment. The cases reported above demonstrate that curare is effective in controlling the most distressing manifestations of tetanus, viz., painful muscular contractions. Whether or not treatment with this drug will lower the mortality rate in tetanus remains to be seen.

Curare acts at the myoneural junction by blocking the transmission of the nerve impulse. This action is due to the inability of the curarized muscle cell to respond to acetylcholine.³ The release of acetylcholine by the neural impulse is not prevented by curare but the response to this chemical mediator is blocked. This blocking is not due to a paralytic action of curare because the involved cells are still capable of responding to electrical and other chemical stimuli.³

The principal dangers in the administration of curare are the development of paralysis of the muscles of respiration, paralysis of the tongue, and the accumula-

tion of mucus in the air passages. In Case 2 muscular relaxation was so marked that the tongue dropped back and occluded the glottis. Mucus accumulated in the respiratory tract and was also a troublesome development.

Our experience with curare in these cases and the limited experience of others as recorded in the literature on the subject lead us to formulate the following statements regarding its use: The chief danger is weakness or paralysis of the muscles of respiration. Therefore, constant attention is mandatory. Neostigmine and physostigmine are physiological antagonists to curare and act immediately to relieve respiratory paralysis induced by it. One of these preparations should be kept by the bedside at all times while curare is being employed. Since these drugs increase bronchial secretions, atropine should be administered concomitantly. Artificial respiration may be life-saving when respiratory paralysis results from treatment with curare. It must be provided promptly and expertly until the curare antagonist, neostigmine, can be administered.

Summary. Two cases of tetanus treated with a curare preparation are reported. The efficacy of this drug in controlling tetanic seizures and painful muscular contractions is confirmed. The management of certain untoward reactions to curare when employed in the treatment of tetanus is discussed.

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CALCAREOUS AORTIC STENOSIS AND CORONARY ARTERY DISEASE*

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THIS study was undertaken to determine the degree of coronary sclerosis that occurs in patients suffering from calcareous aortic stenosis. Similarly the subjective symptoms of the patients were studied to determine to what degree they might be related to the existence and degree of coronary sclerosis.

Procedure. The material chosen for study consisted of the clinical histories and necropsy specimens in 100 cases of calcareous aortic stenosis selected with a view toward getting a representative number of cases in each age group. Stenosis of the aortic valve was graded according to the degree of occlusion of the aortic orifice. Less than 25% occlusion was designated as Grade 1; 25 to

49% as Grade 2; 50 to 74% as Grade 3 and 75% or more as Grade 4. The grading of the degree of sclerosis of the coronary arteries was done in the same manner as was also the grading of aortic sclerosis. In addition the hearts were studied in the gross for evidence of hypertrophy and for the presence of areas of old or recent myocardial infarction.

INCIDENCE OF SYMPTOMS AND SIGNS IN 100 CASES (TABLE 1). *Symptoms.* The most commonly occurring symptom in this series was dyspnea, which occurred in 69 of the 100 cases.

The next most common symptom was angina pectoris, which occurred in 28 cases. The term "angina" was applied only to those cases in which there was a definite history of retrosternal or substernal pain brought on by exertion and relieved by rest. In 10 of these cases mild grades (1 and 2) of aortic stenosis were exhibited while in 18 cases severe grades (3 and 4) of aortic stenosis were exhibited. Of these 28 cases, in 10 an additional complaint of postprandial abdominal distress in the form of mild pain, bloating and "indigestion" was made.

Also in 5 other cases in the series (not associated with angina) there was complaint of postprandial distress. In none of these 15 cases was any associated disease of the biliary or gastro-intestinal tracts demonstrable either clinically or at necropsy.

The symptom of orthopnea was encountered in 26 instances. Dizziness was noted 12 times and the complaint of syncope occurred in only 1 patient.

TABLE 1.—FREQUENCY OF OCCURRENCE OF SYMPTOMS AND SIGNS IN 100 CASES OF CALCAREOUS AORTIC STENOSIS

	Cases
Dyspnea	69
Harsh basal systolic murmur	60
Enlarged heart*	53
Hypertension	29
Anginal type of pain	28
History of tonsillitis	27
Orthopnea	26
History of arthritis	25
History of rheumatic fever	19
Sudden death	18
Postprandial distress†	15
Dizziness	12
Jaundice‡	4
History of chorea‡	2
History of syncope	1

* Compare the incidence of enlarged heart given here with that indicated by the mean heart weights in Table 3. In spite of clinical findings the heart is always found to be enlarged at necropsy even in the milder grades of stenosis.

† Not associated with any demonstrable lesion in the gastro-intestinal or biliary tracts.

‡ In neither of these cases was there a history of rheumatic fever.

* Abridgment of part of a thesis submitted by Dr. Horan to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

Signs. A harsh loud basal systolic murmur typical of calcareous aortic stenosis was heard in 60 patients, an atypical (usually an apical systolic) murmur was recorded in 19 cases and in the remaining 21 no murmur was recorded on the clinical histories.

Enlargement of the heart was noted clinically in 53 cases. Jaundice not asso-

ciated with any clinical evidence of disease of the liver or biliary tract was noted in 4 cases and, in these, other signs of heart failure such as râles or edema were concomitant findings.

Electrocardiographic tracings were made in 52 of the cases (see Table 2). As would be expected the most constant findings were those suggestive of changes in the

TABLE 2.—THE ELECTROCARDIOGRAPHIC FINDINGS IN 52 CASES OF CALCAREOUS AORTIC STENOSIS*

	Stenosis, grade				Cases
	1	2	3	4	
Essentially normal tracing	1	1	1	2	5
Left axis deviation	3	4	4	1	12
Left ventricular strain	2	4	3	6	15
Left bundle-branch block	1	1	3	1	6
Auricular fibrillation	2	1	1	4
Auricular flutter	2	..	2
Right axis deviation	1	2	..	3†
Right ventricular strain	1	2	1	..	4†
Q, T ₃ pattern	1	1

* In these cases inverted T₁ was encountered twenty-one times, inverted T₂ fifteen times and inverted T₃ twenty-one times.

† In these cases there were associated mitral lesions.

myocardium of the left ventricle as exhibited in the 15 cases in which frank left ventricular strain was evident and in the 12 cases in which merely left axis deviation was noted.^{1,9}

PATHOLOGIC CONDITIONS IN THE HEART AND BLOOD VESSELS FOUND IN ASSOCIATION WITH CALCAREOUS AORTIC STENOSIS. *Degree of Aortic Stenosis Contrasted With Degree of Coronary Sclerosis.* It is to be noted from Table 3 that in general, in accord with the findings of Dry and Willius,⁸ there seemed to be a tendency for the degree of coronary sclerosis in this series to be inversely proportional to the degree of aortic stenosis. In 7 cases, obliteration of 25 to 75% of the lumina of the ostia of the coronary arteries was noted and of these 7, angina pectoris occurred in only 2 cases.

Incidence of Hypertension. Hypertension was noted in 29 cases. Of these, results of funduscopic examinations were recorded in 21 cases; 1 of these examinations gave negative results, 2 revealed senile changes and the remaining 18 disclosed typical hypertensive changes. In 3 cases in which hypertension was not de-

tected by the sphygmomanometer, changes in the retinal arterioles characteristic of hypertension were found and in these 3 cases cardiac hypertrophy was noted at necropsy.

In 10 of the cases of hypertension in which characteristic retinal arteriolar changes were evident and in 4 of the cases in which results of funduscopic examination were not recorded, angina pectoris was present.

Associated Myocardial Infarction. Infarction of the myocardium either old or recent was found in 20 cases. In 7 of these the infarction was associated with both hypertension and angina pectoris, in 5 with angina pectoris alone and in 7 with hypertension alone. In the remaining case there was neither hypertension nor angina pectoris.

Cause of Death. Sudden death occurred in 18 cases. Of these, pulmonary emboli were found in 6 cases and 1 patient died apparently as the result of a reaction to plasma transfusion. The remaining 11 patients died either as a result of acute coronary insufficiency or death was in some way associated with calcareous aortic

TABLE 3.—COMPARISON OF GRADE OF AORTIC STENOSIS WITH GRADE OF AORTIC SCLEROSIS, MEAN WEIGHT OF HEARTS, MEAN DEGREE OF CORONARY SCLEROSIS AND INCIDENCE OF OSTIAL NARROWING BY AGE GROUPS IN 100 CASES OF AORTIC STENOSIS

Age (years)	Cases	Aortic stenosis (grade)	Aortic sclerosis (mean degree*)	Hearts (mean gm. wt.)	Coronary sclerosis (mean degree†)	Ostial narrowing (cases)
Under 40	3	3	1	626	1	1
40-49	3	1	2	425	2	
	1	2	2	685	1	
	5	3	1	627	1	
	3	4	2	795	1	1
50-59	3	1	3	427	3	
	10	2	2	494	2	
	7	3	2	655	2	
	4	4	2	596	1	
60-69	7	1	2	455	2	1
	3	2	3	385	2	
	5	3	2	483	1	
	4	4	2	717	2	1
70-79	13	1	3	387	2	1
	6	2	3	476	3	1
	8	3	3	637	2	
	4	4	3	556	2	
80-89	6	1	3	418	3	
	2	2	3	565	3	1
	3	3	3	447	2	
	0	4				

* The degree of arteriosclerosis of the aorta in this series seemed to be dependent on age rather than to bear any direct or inverse relation to the degree of stenosis of the aortic valve.

† All the coronary arteries exhibited some degree of sclerosis.

stenosis.^{2,12,13} The primary cause of death in 42 cases was some pathologic condition of the heart; 58 patients died of other causes.

Comment. Calcareous aortic stenosis is a disease of the aortic valve which usually becomes manifest in later life. Stenosis of higher grades is almost invariably characterized by a harsh systolic murmur over the aortic area together with a coarse systolic thrill palpable anteriorly in the second and third right intercostal spaces; the diagnosis is further substantiated by the absence of the second aortic sound although this latter finding is not necessary for the diagnosis. In the lower grades or milder forms of stenosis the diagnosis may be made by demonstrating calcification of the aortic leaflets or the aortic ring on roentgenoscopic examination. The other diagnostic criteria are well known and need no further discussion.¹⁵

Although in this series a positive history of rheumatic fever was elicited in only 19 cases and a positive history of chorea was

elicited in 2 additional cases, nevertheless the weight of evidence supports the view that calcareous aortic stenosis is a consequence of rheumatic fever.³⁻⁸

The work of others has shown that the lesion in question is usually found in persons in the older age groups.^{8,10,11} Confirmation of this was not possible in the present series since the cases were selected with a view toward getting a representative number of cases in all age groups. However, in selecting these cases for study the impression was gained that in the great majority of all cases of calcareous aortic stenosis the lesion is first discovered when the patient is from 60 to 80 years old.

The relative mildness of calcareous aortic stenosis when compared with mitral stenosis is attested to by (1) the length of time between the actual attack of rheumatic fever and the clinical recognition of the valvular lesion and (2) by the frequency of occurrence of death from non-cardiac causes (more than 50%).

The anginal type of pain which occurred in 28 cases was fairly uniformly distributed not only with reference to the various grades of stenosis but also with reference to the various age groups. The degree of coronary sclerosis on the other hand seemed to be, in a measure, inversely proportional to the degree of aortic stenosis. In all age groups there was more or less tendency for the higher grades of aortic stenosis to accompany the lower grades of coronary sclerosis and for the lower grades of stenosis to accompany the higher grades of coronary sclerosis. No conclusion as to a cause and effect relationship between aortic stenosis and angina pectoris can be drawn from this, however, since it is known that even in the absence of an aortic lesion, necropsy studies in a case in which the patient exhibited a severe anginal syndrome during life may, in rare instances, reveal only minimal coronary sclerosis. Conversely patients who never complained of angina may have coronary sclerosis, Grade 4, which is observed at necropsy.

Hypertension may occur in calcareous aortic stenosis with the same frequency as it does in other organic heart diseases. In this series the incidence of hypertension was 29%; 8 of these patients had Grade 1 stenosis of the aortic valve; 9, Grade 2; 8, Grade 3; and 4, Grade 4. From fundoscopic studies in this series there is no reason to believe that the hypertension associated with calcareous aortic stenosis differs in any way from ordinary essential hypertension since 18 of the 21 pairs of fundi which were studied showed changes typical of essential hypertension. No retinal vessels in the series exceeded a Grade 2 narrowing or a Grade 2 sclerosis. White and Jones¹⁴ in 1928, in a study of 3000 patients with cardiac symptoms, 2421 of whom had organic heart disease, found

the incidence of hypertension to be 29.2% among those with organic disease.

The fact that 10 cases of angina pectoris occurred in association with the less severe grades of coronary sclerosis (but more severe grades of aortic stenosis) and that 18 cases of angina occurred in association with the more severe grades of coronary sclerosis (but less severe grades of aortic stenosis) suggests that the degree of coronary sclerosis does not explain all the mechanisms operating in the anginal syndrome. Other factors to be taken into consideration are: (1) the complete clinical picture which includes such points as age, pain threshold of the patient, presence or absence of an associated disease such as diabetes, hypertension, and so forth, and the presence or absence of a valvular cardiac lesion particularly of the aortic valve; and (2) the complete pathologic picture, which not only includes a study of the coronary arteries and their ostia but also the degree of scarring and hypertrophy of the myocardium and the degree of dilatation of the cardiac chambers.

Summary. A study of 100 cases of calcareous aortic stenosis is presented with particular reference to the degree of coronary sclerosis and the incidence of clinical symptoms and signs.

Some degree of coronary sclerosis was present in every case and this degree was found to be, in a measure, inversely proportional to the degree of aortic stenosis.

The most common clinical symptom was found to be dyspnea which occurred in 69% of the cases.

Of the patients 29% exhibited hypertension and 28% complained of anginal type of pain.

Infarction of the myocardium was exhibited in 20% of the cases.

Sudden death occurred in 18% of the cases.

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A STATISTICAL STUDY OF THE HEMATOLOGIC VARIABLES IN SUBJECTS WITH THALASSEMIA MINOR*

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THALASSEMIA¹¹ (Cooley's anemia, Mediterranean anemia) is an inherited hematologic disorder which, as its name implies, is limited almost entirely to racial groups originally living around the Mediterranean Sea. In the United States it is not infrequently seen in immigrants of Mediterranean stock and in their descendants. The disease exists in 2 forms: the severe, progressive, and almost invariably fatal form originally described by Cooley and Lee,¹ and the genetically related but milder form which has been the subject of numerous reports in the medical literature of recent years.^{2,3,7,8,9,10,12,13} It has been suggested that the term "thalassemia major" be applied to the former and the term "thalassemia minor" to the latter.¹⁰ This is in keeping with the close genetic and hematologic relationship of the 2 conditions,^{3,6,10} and indicates that while they are qualitatively essentially similar, quantitative differences in severity exist. Thalassemia major occurs about one in each 2400 births to persons of southern Italian or Sicilian stock in Rochester, New York, while thalassemia minor occurs about once in 25 such births.⁵

The more qualitative hematologic characteristics of thalassemia minor are becoming well recognized. It is a condition distinguished by the occurrence in well-nourished persons of hypochromic, microcytic erythrocytes, not infrequently oval in shape or appearing as "targets" on the stained blood smear. Basophilic stippling is common. The hemoglobin values and volume of packed erythrocytes are usually

but not invariably below the normal range. By comparison the total number of erythrocytes is disproportionately high. The erythrocytes characteristically show increased resistance to hemolysis by hypotonic saline. There may or may not be leukocytosis, reticulocytosis and elevated icterus index, or splenomegaly. In Italian subjects with thalassemia minor studied in Rochester, New York, leukocytosis and elevated icterus indices have been unusual and reticulocytosis of only slight degree.

The present report represents a statistical analysis of the hematologic findings in 82 subjects with thalassemia minor and is prompted by the apparent desirability of further clarification of the more quantitative aspects of this not uncommon disorder of the Mediterranean peoples. The data on which the paper is based have been compiled almost entirely from Italian subjects residing in Rochester, New York, or its environs and have been presented in part in previous publications.^{6,10} In most instances these subjects were from southern Italian or Sicilian stock. In order to evaluate more adequately the hematologic defect, there are included similar studies on normal members of family groups in which thalassemia occurs. These normal individuals presumably share the same hereditary and environmental background as the subjects with thalassemia minor and are therefore especially suitable for comparison.

Methods. The hematologic studies were in every case made by one or the other of

* The major portion of the observations on which this paper is based were made while the authors were associated in the Department of Medicine of the University of Rochester School of Medicine and Dentistry and the Medical Clinics of the Strong Memorial Hospital and the Rochester Municipal Hospital, Rochester, New York.

the authors. All blood samples were obtained with careful attention to avoiding stasis or hemolysis and were placed in bottles containing both potassium and ammonium oxalate in the proportions suggested by Heller and Paul.⁴ In blood so collected there is no alteration in the volume of the erythrocytes. In almost all instances erythrocyte counts were done in duplicate and averaged. Only Bureau of Standards certified equipment was used. Hemoglobin determinations were made according to the method of Sahli employing carefully calibrated hemoglobinometers. The volume of packed erythrocytes was determined by centrifuging a properly filled Wintrobe hematocrit tube at 3000 r.p.m. for 1 hour. No subject in which there was any question

of the diagnosis was included in the analysis. Similarly no subjects were included in which known coexistent disease might distort the blood findings. In the majority of instances family group studies were made.

PRESENTATION OF DATA. The data are best presented in tabular and graphic form. Table 1 indicates the means and standard deviations of the hematologic variables subjected to analysis. The data is broken down into different age groups since well-recognized physiologic variations from normal adult values are found in children of different ages. In the adult groups females and males are analyzed separately. In all groups 14 years of age

TABLE 1.—MEANS AND STANDARD DEVIATIONS OF HEMATOLOGIC VARIABLES FOR NORMAL AND THALASSEMIC SUBJECTS FROM THE SAME ITALIAN FAMILY GROUPS

Aged	Group	N	Hemoglobin (gm. %)		R.B.C. (millions per c.mm.)		Volume of packed R.B.C. (%)		M.C.V. (μ)		M.C.H. (m μ)		M.C.H.C. (%)		% saline at which complete hemolysis occurs	
			Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ
1-4	Normal	5	13.1		4.56		37.9		83.5		29.1		34.5		0.30*	
	Thalassemic	9	11.4		5.72		36.4		63.8		19.9		32.4		0.21	
5-9	Normal	3	13.6		4.72		39.9		84.8		29.1		34.1		0.30	
	Thalassemic	6	11.7		5.88		37.4		64.0		20.0		31.3		0.23	
10-14	Normal	4	14.2		4.70		40.9*		84.2*		30.4		35.7*		0.31*	
	Thalassemic	9	12.0		5.95		37.3		63.8		20.6		32.3		0.22	
Adult males	Normal	21	16.2 \pm 1.27		5.27 \pm 0.550		45.8 \pm 2.42		87.6 \pm 6.13		30.9 \pm 2.35		35.3 \pm 1.89		0.31	\pm 0.022
	Thalassemic	27	13.5 \pm 1.35		6.12 \pm 0.620		42.1 \pm 3.50		69.0 \pm 4.97		22.0 \pm 1.73		32.0 \pm 1.59		0.23*	\pm 0.027*
Adult females	Normal	21	14.1 \pm 0.90		4.67 \pm 0.414		40.6 \pm 2.19		87.4 \pm 5.81		30.4 \pm 2.29		34.7 \pm 1.37		0.31	\pm 0.014
	Thalassemic	31	11.8 \pm 1.15		5.59 \pm 0.430		37.3 \pm 2.88		67.0 \pm 6.02		21.2 \pm 2.29		31.7 \pm 2.00		0.23	\pm 0.029

All age groups with the exception of adults include both males and females.

N, number of subjects. σ , standard deviation.

* Based on 1 less than N.

or younger females and males are grouped together. The numbers included in certain age groups are so small as to render statistical constants of little significance.

Figure 1 indicates graphically the populations of hemoglobin values for individuals with thalassemia minor as compared with individuals from the same family and racial groups not having thalassemia minor. In both the normal and thalassemic groups females are designated by a different symbol than males.

Figure 2 shows the % of individuals above 15 years of age having hemoglobin values within the arbitrarily designated ranges. The control figures given were as in Table 1, derived from the non-thalas-

semic members of the same family groups.

Figure 3 indicates the % of individuals having erythrocyte counts within arbitrarily designated ranges. The data are analyzed for the same individuals and in the same manner as in Figure 2.

Discussion. The present analysis serves to underline and to quantitate some of the already recognized features of thalassemia minor. It can readily be seen from the table and figures that individuals with this condition have a definite and significant hematologic defect in comparison with normal members of the same family groups, and this difference is already well established in childhood. On the average in adults of both sexes this defect amounts

to a deficiency of 2 to 3 gm. of hemoglobin per 100 cc. of blood. It is also readily apparent that this defect is superimposed on the normal patterns of male and female blood pictures. Thus males with thalassemia minor showed substantially higher hemoglobin values than did females similarly affected. This difference was of the same order of magnitude as differences observed between normal males and females in the same study.

The marked tendency for all individuals with thalassemia minor to have an elevated erythrocyte count is strikingly shown in Table 1 and Figure 3. The mean values for erythrocyte counts in both females and males are well above those found in normal individuals even in the face of the substantially low hemoglobin values. This tendency to "polycythemia" has been commented upon before but in Rochester Italians it is almost uniformly a characteristic part of the pattern. Thus, including both males and females only 2 out of 58 adults with thalassemia minor has erythrocyte counts below 5,000,000 per c.mm. In 48.3% of thalassemic females and 85.8% of thalassemic males the counts were above 5,500,000 per c.mm. The tendency to "polycythemia" was, as might be expected, more prominent in

males, 57% of whom had red cell values in excess of 6,000,000 per c.mm.

The mean corpuscular volumes and mean corpuscular hemoglobins are, of course, markedly below normal. The mean corpuscular hemoglobin concentration is, on the other hand, not nearly so markedly lowered as are the first 2 constants. This means that while the individual cells are of markedly low volume and hemoglobin content, each cell *for its volume* is only moderately deficient in hemoglobin. Stated otherwise, each unit of cell contains only moderately less hemoglobin than each unit of a normal erythrocyte, but the cells themselves are small in volume.

It must be remembered that the data presented are based on studies made from relatively homogeneous racial stock in a single American city. The individuals studied are almost uniformly of southern Italian or Sicilian extraction. It may be that racial factors alter the characteristic pattern in other Mediterranean peoples. The data probably represent a suitable cross-section of the usual hematologic findings in the racial groups studied.

The biologic significance of the degree of hematologic defect exhibited by indi-

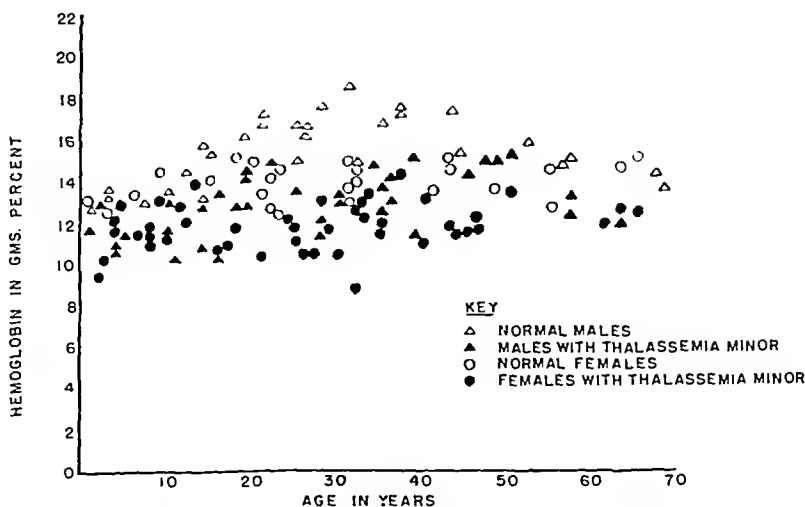


FIG. 1.—Individual hemoglobin values observed in normal and thalassemic members of the same family groups.

viduals with thalassemia minor has been discussed in a previous report.⁶ It is difficult to assess but most probably these individuals have approximately the same handicap as an individual with iron defi-

ciency of comparable severity. Just what the defect means in terms of meeting such increased hematopoietic demands as pregnancy, blood loss, and infection is not now known.

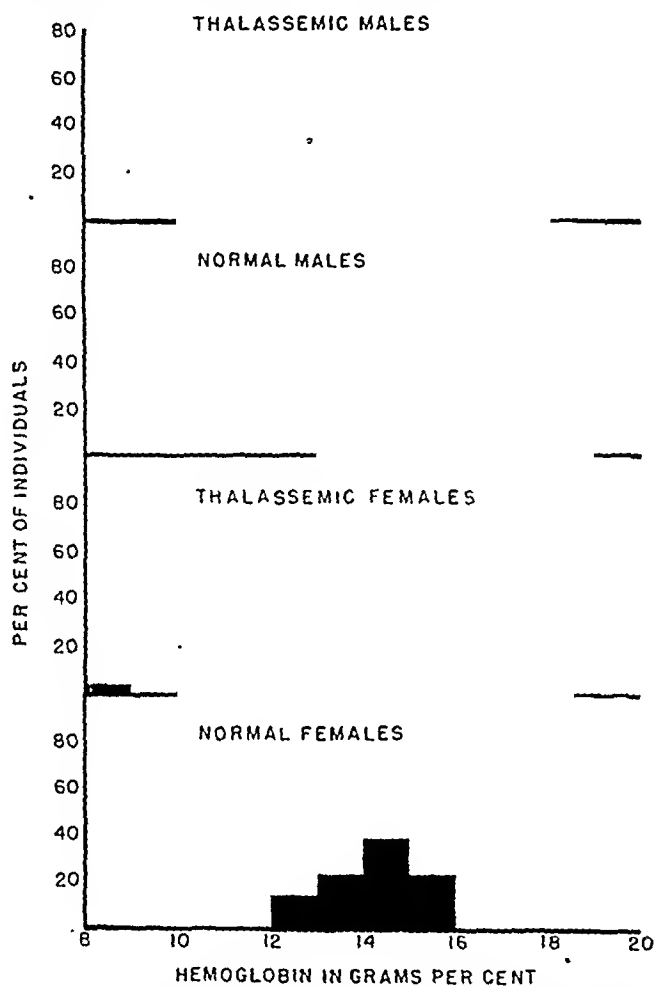


FIG. 2.—Per cent of normal and thalassemic individuals from the same family groups having hemoglobin values within various designated ranges. Only individuals 15 or more years of age are included

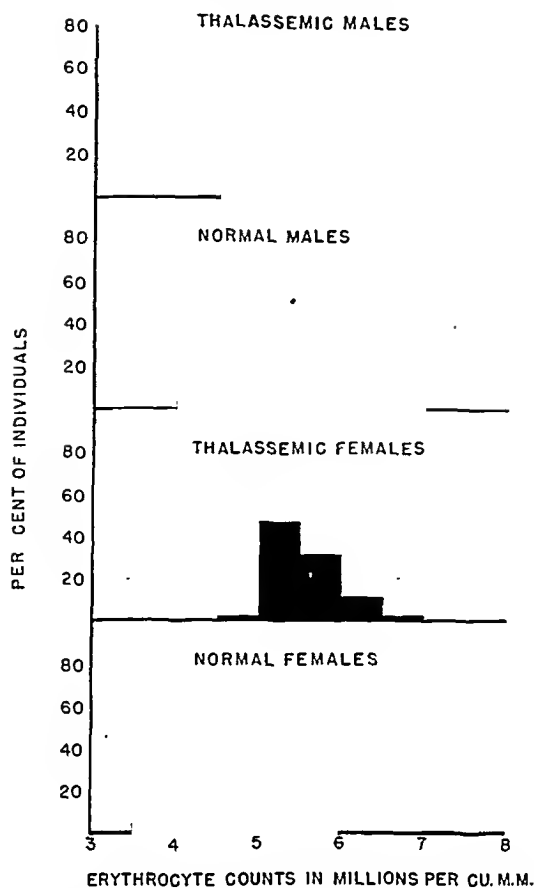


FIG. 3.—Per cent of normal and thalassemic individuals from the same family groups having erythrocyte counts within various designated ranges. Only individuals 15 or more years of age are included.

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PROGRESS OF MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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SOME PROBLEMS IN THE BIOLOGY OF THE SYPHILITIC INFECTION

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GREAT advances in the therapeutics of a disease have an unfortunate tendency to discourage fundamental research, and to create an impression even among critical minds, that the disease in question being now "in the bag" there is no further occasion for hunting. In the case of syphilis, and indeed of all the venereal group of infections, such a reaction is particularly unfortunate; for these diseases carry in their own biology and clinical course the means of their indefinite perpetuation. The inconspicuous onsets, and prolonged period of infectivity in which little incentive to diagnosis and treatment exists, as well as the margin of non-cure (still existent in syphilis at least) assures the transmission of the infection to fresh individuals, and the maintenance of a reservoir. Before the venereal diseases are conquered an immunizing procedure must be developed, a vaccination of high if not absolute effectiveness, to protect the originally uninfected person through long periods if not through life; and to prevent reinfection, which is now suspected of being a

loophole through which magnificent cure possibilities leak away to relatively unsatisfactory epidemiologic results.

The field of needed research is a large and inviting one, to which, for example, 2 recent reviews by Beerman^{1a,b} have directed attention. The clinical mechanisms underlying the symptomatology of syphilis are so far from understood as to justify the maintenance for years of clinical centers for the study of such problems as the nature of latency, the meaning of serologic tests in relation to the biology of the disease and its cure, the non-specific mechanisms of bodily reaction (serologic false positives) and of defense against infection. The calm assumption that reagin is a substance; that antisiphilic drugs exert their entire effect directly upon the organism of the disease without the intervention of intermediate agencies provided by organ and tissue function in the host, and by cellular and biochemical (even enzymatic) agents indispensable to therapeutic effect, are familiar examples of syphilologic naivete. The only intermediates thus far given even a hearing

have been Levaditi's bismoxyl, glutathione and most recently the "spreading factor," hyaluronic acid. The basis of crippling symptoms such as the lightning pain and the gastric crisis of tabes, both often at their worst after the serologic signs of activity of the disease have been reduced to negative is wholly unknown. More than 40 known conditions give rise to a serologic reaction in the blood similar to that of syphilis; almost nothing is known about the false positive in the spinal fluid. All the therapeutic agents used in syphilis, including mercury, bismuth, iodide, the arsenicals, penicillin and fever are effective against conditions as widely different from syphilis as lichen planus and subacute bacterial endocarditis. Disease due to fungi, to a wide range of bacteria, to protozoa, and to the allergic state, responds and under some circumstances fails to respond to treatment for syphilis in as yet unexplained fashion. Many of the clinical problems presented by syphilis particularly in the field of infection allergy are capable in their study and solution, of throwing much light on human diatheses which are still obscure. Even the influence of climate has its important syphilologic aspects, side by side with diet and endocrine balance and function. Such statements only touch the surface of the possibilities.

It is evident then that to the investigator with intestinal fortitude and ingenuity, there is no excuse for retiring from the clinical or the experimental field offered by syphilis. The purpose of this review, to some extent supplementary to Beerman's^{1a,b} is to indicate directions, particularly in the study of the causative organism, in which the demand for more work is imperative.

Before opening the discussion, it is well to call attention to 2 basic investigational warping factors that are sometimes underestimated. They crop up in the proceedings of meetings more often than in the actual literature. These are the interpretation of *in vivo* as compared with

in vitro results, and the transfer of inferences based on animals, directly to the behavior of man. Bottled and test-tubed spirochetes are by virtue of their lack of virulence, an artificial product, whose very identity is often controversial (discussion of the Reiter strain, for example). The asymptomatic infection of the rat and the symptomatic disparities between the course of syphilis in the rabbit and in man particularly with reference to the more serious late manifestations are illustrations of vital differences in behavior and host parasite relationships that affect final conclusions on the applicability of experimental results to man.

CULTIVATION OF VIRULENT *TREPONEMA PALLIDUM*. It is generally conceded that this ultimate and fundamental desideratum has not been achieved. The problem of cultivation alone, whether of virulent (animal to medium) organisms or of long-standing avirulent strains is highly complex and involves control factors easily overlooked. Frazier mentions the maintenance of anaërobiosis as becoming increasingly difficult as the use of turbidimetric methods of estimating growth are applied (*c. g.*, agar cannot be used as the basic medium). Whiteley and Frazier⁴⁸ used sodium thioglycolate as the agent of choice. These investigators rate albumin as the common essential ingredient of the fluid constituents of spirochetal culture media. From this point, working with the Reiter strain, they have succeeded in producing a clear medium with only known chemical ingredients which satisfies the nitrogen, carbohydrate and vitamin requirements for the growth and subculture of the Reiter strain of *T. pallidum*. From such a stable controllable base as this, the problem of what constitutes or fosters growth and perhaps virulence in a culture medium can presumably be attacked.

Approaching the problem from a different direction, are the attempts to grow virulent *T. pallidum* in the chick embryo as described by Sterzi and Staudacher,³⁷ Callaway and Sharp,⁶ Wile and Snow⁵³ and Wile and Johnson.^{50a} None of this

work has progressed farther than to show that *T. pallidum* can be kept alive and virulent in the chick embryo for periods ranging from 2 hours to 8 days (1 experiment in 5). Evidently the conditions are in the main adverse under present techniques, and the fact of growth has not been demonstrated. Steinhaus and Hughes³⁶ have found an unknown spirochete in hen tissue and chick embryos as a complicating interpretative factor. The preservation of virulence under freezing conditions has been demonstrated by Turner^{42c} up to 1 year in solid CO₂ and alcohol at -78° C., and has its application in the use by Magnuson *et al.*²¹ in attempted immunization by lyophilized organisms (see below). Probey³² has recently reviewed the existing literature on the viability and virulence problem in lyophilized serum and has shown that *T. pallidum* becomes avirulent during the deep-freezing and drying process. Bessemans^{2b,c} and Kast and Kolmer¹³ have called attention to morphologic change in *T. pallidum* as it adapts itself to life in culture as against life *in vivo*, the thicker forms and flatter curves being associated with culture and the thinner more mobile forms with the struggle for existence in tissue.

Speaking with the presumption of clinicians on offering suggestions on laboratory problems, it would seem to us that the problem of virulence will be advanced toward solution by (1) a study of morphologic differences between virulent and avirulent living spirochetes to which the electron microscope lends itself; (2) development of a technique of mass cultivation of avirulent spirochetes such as has so substantially advanced the study of the chemistry of the tubercle bacillus and the pneumococcus; (3) mass isolation of large numbers of virulent *T. pallidum* from giant syphilomas (granuloma tissue chancre) in rabbits for chemical studies; (4) study of the effect of changes in the chemical and physical constitution of media on morphology, longevity, motility and ultimately virulence of both virulent and

avirulent spirochetes; (5) and passage of *T. pallidum* through specific tissues to modify its virulence and to develop tropisms; this to include utilization of tissue culture and tissue extracts, and even hormones for such purposes.

THE SYPHILITIC ULTRAVIRUS PROBLEM. The existence of some form of ultramicroscopic agent in the pathologic mechanisms of syphilis has long seemed a theoretical necessity. Conspicuous among the phenomena to be explained are the apparent absence of spirochetes in infective lymph node material, the paucity of spiral organisms in the tissues of latent infections, and in late syphilitic granulomas, whose infectivity could only be demonstrated by animal inoculation. The attempts to prove an explanation have involved the assumption of a life cycle for the organism, with a difficultly demonstrable granular or resting stage; and the positing of an ultramicroscopic, filter-passing transmutation form of virus, alternative to the spirochetal form so long familiar in dark-field and tissue preparations. Pre-World War II investigators busied themselves mainly with observations and theorization regarding a life cycle (Warthin and Olsen,^{46a,b} Ingraham¹¹ and Stokes.³⁹) The post-war studies have shown a swing toward the virus type of hypothesis, under the impetus furnished by the electron microscope, by the studies of mouse-brain filter-passing inocula and indirectly by demonstrations or announcements in other fields of the transmutation of other bacteria (*Eberthella typhosa*, streptococci and of *Leptospira icteroides*) from a visible to an ultramicroscopic form. It would seem specially important that such announcements as those of Kendall¹⁴ and of Rosenow and Oftedal^{34a,b} on virus or ultraviolet transmutations by alteration of growth media be put to the test on existing strains of spirochetes as soon as such studies as those of Whiteley and Frazier⁴⁸ have led to a synthesizable and controllable growth medium. Meanwhile the electron microscope has demonstrated intraspillar granules and confirmed the

existence of the spore-like bud or knob described by investigators on microscopic evidence. It may well be hoped that the mode of reproduction of spirochetes will now be clarified, including the long-desired proof of growth of a spirochete from a Meiwsky^{26a,b,c,d} or argentophile or spirochetogenic granule. Whether the intrafilamentous granules demonstrated by the electron microscope in the photographs of Mudd *et al.*,^{28,29} Morton and Anderson,²⁷ Wile and Kearney,⁵¹ Wile, Picard and Kearney⁵² are degeneration products of a virus transmutation may perhaps also be determined (*Cf.* Levaditi^{16b}). Bessemans *et al.*,³ long a vigorous opponent of the ultramicroscopic phase concept, has attacked the problem with a micromanipulator with as yet inconclusive results. Levaditi^{16a,17} considers the evidence of the existence of an ultrafilterable virus inadequate, on the basis of experiments in the infectiousness of the suspensions passed through collodion membranes of various meshes. He concludes that the syphilitic infectious agent will not pass meshes which should pass true ultraviruses. In a comparative study of several species of spirochetes, Séguin³⁵ believes he has proved that the conversion of a filter-passing spirochetogenic granule into a spirochetal filament is a common transformation among spirochetal organisms.

Johnson and Wile's⁵² observations on the infectivity of filtered mouse-brain suspension in "carrier" mice are of particular interest as defining some of the conditions under which transmission in the absence of visible spirochetes and under various grades of filtration may take place. Johnson and Wile's experiments showed that mouse-brain added to infective suspensions of syphilitic rabbit testicle inhibits their infectiousness, and that infectiousness of mouse-brain tissue itself is lost by passage through a coarse Mandler filter.

These 2 investigators had previously proved that mouse material capable of transmitting the disease contained neither spirochetes nor histologic changes char-

acteristic of syphilis. Wile's⁴⁹ most recent study indicates that the non-visible agent can be carried through as many as 4 passages from mouse to mouse without becoming visually demonstrable and that the pooled suspension of mouse liver, spleen and gonads in which it is present retains its virulence longer than does the brain emulsion.

In the summary of the invasion mechanism given below, mention will be made of studies in the minimum inoculum of spirochetes that will transmit the disease, which offer an explanation based in the infection potentiality of small numbers of spiral organisms, the alternative conception of an ultravisible form, to account for transmission by apparently spirochete-free suspensions.

The search for spirochetal forms and derivatives, and a possible ultravirus in tissue is making slow headway. Stroesco and Vaisman,³⁸ in Levaditi's laboratory, have developed a silver impregnation method applicable to frozen section only, by which it was shown that spirochetes are demonstrable thus far only in infected mice of the first generation, and are few in number. They are not present in second and later inoculations. Lépine told Wile in a personal interview that these spirochetal forms were in his opinion non-virulent and that he believed, from a large experience, the infection was carried from mouse to rabbit by an invisible or granular stage of the organism. The development of freezing microtome methods producing exceedingly thin sections and frozen dried preparations (Wycoff^{54a,b}), and using satisfactory high-speed microtomes already commercially available, should make possible the liberation of the search for spirochetal life cycle forms and for the ultravirus in tissue from some of the artefacts or alleged artefacts in fixed and stained tissue confusable with them. The boldest expression to date on the matter of ultravirus in tissue from late syphilids was a recent statement of Rakhmanov and Mashkilleison³³ before a local Philadelphia

meeting—that of the Philadelphia Chapter of the American-Soviet Medical Society on Sept. 24, 1945, which, however, in the *American Review of Soviet Medicine*, was toned down to an “under investigation” level. The best summary currently available of *T. pallidum* life cycle or other variants in tissue is that of Olsen,³⁰ one of Warthin’s pupils and co-workers.

THE INVASION MECHANISM. *Via* the grapevine and cloakroom discussion at meetings, it is becoming clear that the transmission of syphilis, not to mention gonorrhea, to man by inoculation even by the “normal” mechanism of sexual exposure to infected contacts is not a simple or unvaryingly successful affair. It has long been suspected that the rise and fall in the incidence of syphilis in populations and countries is conditioned by other factors than the mere prevalence of infective exposure; but apart from some guesses as to the rôle of immunity conveyed by the peak of the preceding “epidemic” wave, in producing a fall of incidence, no conception of the mechanism of resistance to infection has arisen. It is to be hoped that the details of experience in the Guatemala project under Mahoney’s²³ direction will not be withheld from publication by diplomatic or other considerations.

Pending further information on factors governing resistance to invasion, the increasingly clear demonstration and accurate timing of the spread of spirochetes from their inoculation site should be noted. The data reviewed by Turner^{42d} and the observations of Levaditi, Vaisman and Rousset-Chabaud¹⁸ which are couched in terms of days, are merely confirmatory of the painstaking work of earlier investigators including Brown and Pearce.⁵ Kolle and Evers¹⁵ brought the time of dissemination from inoculation site to regional lymph node down to minutes, the average of several investigators’ results ranging around 35 minutes (Bessemans,⁴ Levaditi¹⁹ and others). Mahoney and Bryant²⁴ showed that actual invasion of the intact mucosa of the preputial sac

of the rabbit required 3 to 4 hours, but they were obliged to use cotton packs impregnated with the spirochetal emulsion, a situation hardly comparable to “physiologic” inoculation. It may be seen that in all this experimental work, now a decade or more old, little has been accomplished toward the delineation of the conditions in man under which infection does or does not follow exposure. Frankl⁹ as well as Charpy⁷ showed that the *T. pallidum* can be present in the normal skin of syphilitics without providing any of the histologically recognizable stimulus to lesion formation.

That the size of inocula, that is, the number of treponemes by actual count, influences invasion and infections as far as symptomatic character is concerned, has been one of the interesting developments of the decade. The studies all suffer from a common element of uncertainty in that they accept the spiral organism as the infectious element and give no consideration to the possibility of an accompanying ultramicroscopic invader (see summary above on mouse-brain inoculation). In 1943, Thomas and Morgan⁴¹ carried out pioneer experiments on isolation and attempted inoculation of single *T. pallidum* obtained under dark-field with the Chambers micromanipulator. They failed to secure infection with doses of 1 to 6 organisms. They concluded, however, that a negative tissue transfer does not preclude the presence of *T. pallidum* in the inoculum or the absence of syphilis in the source animal. As a condition on the use of lymph node transfer, as a test of infection one must now recall the reported statement of Bessemans made in discussion of Moore before the Microbiological Congress, in Copenhagen (1947), on criteria of penicillin cure, that a transfer may be negative at 6 months but positive after 2 years.

The whole subject of inoculation on mechanism has been materially advanced by the presentation at the April 1947 symposium on Recent Advances in the Investigation of Venereal Diseases, Wash-

ington, D. C., of the observations of Magnuson, Eagle and Fleischman²⁰ on the minimal infectious inoculum of the Nichols strain of *T. pallidum*. This study reviews the literature, goes carefully into the mathematic estimation of the error of the methods employed by the authors and reaches the conclusion, contrary to Thomas and Morgan's, that 1 or 2 treponemes per inoculum are regularly infectious for 47% of rabbits intratesticularly inoculated. Two treponemes introduced through the skin are infectious for half the inoculated animals. A gradually ascending percentage gradient of successful inoculation was demonstrated as a function of increasing size of inoculum, up to 100% with 200,000 organisms. The incubation period of the animal infections was the same for inocula from 1 to 100 organisms (35 to 41 days) but fell sharply above that level to 27 days with 10,000 treponemes and 17 days with 200,000. The study indicates the importance of time factors in removal and inoculation, and the concentration of serum and tissue extractives in the inoculum.

Again, without minimizing the great importance of such tangible experimental results, it must not be forgotten that they deal with inoculation and invasion conditions probably quite different from those prevailing in the "natural" inoculation of man.

THE ASYMPTOMATIC INFECTION AND CARRIER PROBLEM. "Is a lesion and in particular a spirochete-rich lesion, essential as source to the human-to-human contact transmission of syphilis" phrases the eminently practical form that this problem takes in the epidemiology of the disease. "Can an asymptomatic individual transmit the disease?" and "What is an asymptomatic infection?" are 2 practical collaterals that must be constantly kept in mind. The late Dr. Warthin never tired of insisting that latency is a combination of undercover activity and of reactionless symbiosis, for which he used the "miliary gumma" or microreaction in the wall of the aorta (whose ability

to produce animal inoculation syphilis has recently been demonstrated by Hu, Liu, Chen and Frazier¹⁰) and the hordes of treponemes in the apparently normal muscle of the heart of the congenital syphilitic, as respective illustrations.

Bessemans^{2a} has provided one of the best summaries of the essentials of asymptomatic infection in the rabbit, still weighty after a decade, and quotable from the abstract in *Venereal Disease Information* as follows: "He finds that there are a number of factors involved, some of them in the parasites and some in the host. The number of cases of asymptomatic syphilis is increased by anything that limits the virulence of the parasites. Young strains, for instance, cause a higher percentage of asymptomatic cases than older ones, as if the progressive adaptation of the parasite to the host increased its virulence. The number of parasites used seems also to have an effect, though there seem to be exceptions to this rule, and there are cases in which asymptomatic syphilis is not produced by the lowest dilutions. Intratesticular inoculation generally causes a manifest syphilis, while inoculation into certain other tissues of the rabbit, such as the nervous system, the suprarenal capsule, the blood, the skin, and mucous membrane, the eye, and the kidney only causes symptomatic syphilis. There are certain individual differences in the animals. Adult female animals show a higher percentage of asymptomatic syphilis than young males. When the animals are in poor general condition, the percentage of asymptomatic cases is greater. A high temperature in the tissue tends to increase the number of asymptomatic cases. Dujardin claimed that the number of cases of asymptomatic syphilis is influenced by the allergic condition of the animals. The author tested this statement and did not find that allergic hypersensitiveness had any relation to the number of asymptomatic cases. However, he thinks that this question of an allergy

requires further study before a definite opinion can be pronounced."

Once it is possible to isolate with the micromanipulator individual treponemes in the symbiotic state from tissue (as in Frankl and Charpy's observations) and to test their virulence for animals, we shall have made a first step toward the basic interpretation of the carrier state and the question of tissue reaction in its relation to virulence. In this connection much of Besseman's statement should be kept in mind along with Johnson and Wile's^{50b} observation on the virulence inhibiting qualities of mouse-brain tissue, etc.

ASYMPTOMATIC INFECTION AND THE CARRIER STATE. A number of recognized facts have tended in the biology of the syphilitic infection, to dissociate infectivity and virulence of the organism from the mechanisms of microscopically visible tissue reaction in the form of lesion development and of lesion involution and healing. The identification of a carrier state in the rat has been followed by its demonstration in the white (albino house) mouse and other species of mice; and in several species of hamsters. These animals are then so far as visual evidence of syphilis is concerned merely test-tubes. The golden hamster^{50b} does not even develop a positive seroprecipitation reaction (Kahn test) for the disease. Search of the organs and infective tissue material (Weller, quoted by Wile⁴⁷) reveals neither demonstrable tissue changes of syphilitic type nor spirochetes by the Warthin-Starry silver impregnation. Yet the infection is transmissible to rabbits in practically all instances by such material. In the Jacobs and Heidelberger series of chemotherapeutic pentavalent arsenicals which led to tryparsanide, a compound was prepared which caused rapid healing of the lesions without destruction of spirochetes.⁴⁰ In fact, they flourished, and the animal infection generalized while the lesion vanished. Whole schools of thought such as the French pediatric group, led by Hudelo, have implied the clinical existence of man of asymptomatic mass in-

fection with vague constitutional consequences to the third and fourth generation. The tie-in of the animal asymptomatic state with size of inoculum seems generally accepted (see above) and few enough organisms gaining entrance can lead to prolongation of incubation period and absence of demonstrable lesions. Pariser,³¹ who has provided a full review of this literature, examined directly the transmissibility of syphilis by the genital mechanism in a study of the infectiousness of semen and of vaginal secretions in the human, in which he found that the semen of the male is not infectious unless a spirochete-containing lesion is present in the tract, and the vaginal secretions are not infectious unless there is an abnormal cervix (or by implication also a uterine lesion) or the woman is menstruating. How consistent over the life span of such an individual this non-infectiousness as a carrier may be requires much further study. What Pariser has shown thus far would seem to be that in the human subject asymptomatic infection does not exist, but only an asymptomatic state punctuated by symptomatic interludes. If there is any way other than by the development of lesions or by discharge through blood or physiologic secretions that the infective agent can be released from the asymptomatic body test-tube, it is as yet unknown. It might be studied with a little better chance at solution by maintaining uninfected and infected injured and uninjured individuals in contact and by interbreeding infected and uninfected animals such as the hamster.

The clinical evidence for a genuinely asymptomatic state in the human subject involves such problems as the unaccountable but persistent high-titer serologic test for syphilis. Such tests are now complicated by all that is known and not known about the specificity of serologic tests; and by the type case of an asymptomatic but faintly stigmatized or "suspect" victim of what may be a congenital infection as the only one in a large family

otherwise free from evidence of the disease.⁴⁰

IMMUNIZATION AND IMMUNITY-SUSCEPTIBILITY PROBLEMS. The clinician and the public health officer, viewing ruefully the inverse relation between the spread of venereal disease and its increasingly ready response to an increasingly simplified treatment, realizes that in the direction of immunization lies the most important single hope for the extinction of syphilis. The difficulties of the problem can be imagined from the foregoing discussions of the biologic mechanism. It is therefore small wonder that so little systematic effort has been expended on the problem. One must first clarify innumerable problems, recently reviewed by Urbach and Beerman⁴⁵ in their discussion of immunity and allergy in syphilis. Not the least among them is the still unsolved problem of the manifestations induced in late syphilis by the injections of spirochetal suspension, purified or tissue-free, and suspended in tissue menstrua. One becomes entangled with a non-allergic phase of reaction, as in ordinary luetin tests and with homologous and pseudoreactions induced by such agents as potassium iodide, in late syphilis and congenital syphilis especially. There is needed, too, a much more precise understanding of the anergic or tissue non-reactive state in syphilis in its relation both to host and to spirochetal constitution.

Nonetheless, bold attempts to leap the fence of unknowns deserve vigorous commendation and support, in the hope that a new Jenner may arise among us. The work of Turner and his associates^{8,25,42a,b,c,43,44} has included studies of yaws and the *T. pertenue* and *T. cuniculi* as well as *T. pallidum*. His most recent paper⁴⁴ reports the development of various degrees of cross-protection against infection by these 3 organisms in the rabbit. The recent papers of Magnuson and co-workers^{21,22} deal with the rate of development of immunity to infection in the rabbit and currently²¹ with an attempt at immuniza-

tion of rabbits against killed *T. pallidum* and adjuvants (*M. phlei* emulsion in oil). The attempt at immunization was a failure, although the animals developed positive serologic tests for syphilis. The method of testing transmission was that of lymph node transfer, which is not free from objection.

The use of spirochetal vaccines for the treatment of syphilis including the Hilgermann preparation of supposedly *T. pallidum* has been reviewed by Urbach and Beerman with the statement that no significant conclusions have thus far been established. The conditions for which it has been used are all known to respond to treatment of low specificity like that of gumma to iodide.

The sketchiness of our knowledge of even this selected list of problems in the biology of syphilitic infection leaves an indelible impression of the need for further and still more ingenious research. Among the categories of unsolved problems one should list in addition to those above considered, the matter of strains and elective localization; the possible tropisms of the organism; the host side of tropism or tissue susceptibility and immunity which might be studied by tissue culture; the problems of infection allergy; and the defense mechanism of the host, including specific cell function within the tissue reaction against the infection (*e. g.*, the lymphocyte and the plasma cell), and the influence of the spreading factor on the course of a syphilitic infection. From some of the observations on the serologic responses of vaccines it is only a step to the study of the nature, and the question even of the existence, of specific reagin as a chemical entity. The exploration of the non-specific reactive mechanism of serologic tests is only in its beginnings. May it not be conceived that reagin will turn out to be not a substance but a ratio, and the serologic reactive mechanism of the body a type form or habit of reaction induced by a variety of agents, chiefly infectious in origin?

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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FACIAL RESTORATIONS IN MEDICAL PRACTICE

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A PROsthESIS (πρόσθεσις), a putting to, from προστιθῆμι, to put to) is an artificial substitute for any missing part of the body. Since most such corrections are for facial deformities and defects, much of the literature and the interest is concerned with facial restoration.

As described by Brown,¹ prostheses should be looked on as of 2 types: 1. The type indicated when surgical intervention is contraindicated. Here are included cases in which coexisting disease or other disability makes surgical treatment inadvisable and cases in which surgical manipulation of the tissue would end with esthetically undesirable results.

2. The second type of prostheses (which Esser has called the "bloody" type) are those which necessitate surgical incisions for their establishment. The sculpturally molded synthetic implants come under this heading. What is the difference between the synthetic materials here described and the previously used ivory, celluloid and cartilage? These materials are molded from sculptured models; they do not slip out of place, since they fit only 1 area; they do not curl and will not shrink, nor have they been found to be a source of irritation of tissue because of composition.

The appearance of new literature to describe artificial substances and the technique of building these materials as substitutes for missing parts of the body indicates the limitations of materials that plastic surgeons have had to work with. Problems of the shape of the cartilage and

the bone of the donor, of the absorption of the transplanted living material and of hand molding of cancellous bone have limited the sculptural effects otherwise possible in plastic surgery.

But really clever implantation techniques have been devised by imaginative surgeons. The diced cartilage technique for the filling of defects under the skin is one of these. Yet there is a need for further versatility in the adoption of useful implantation materials.

Prosthetic implants of ivory, celluloid, steel and tantalum are a partial fulfillment of the need for such materials. The newer synthetic resins, those which can be polymerized to a state of biologic inertness, promise immense advantages in this field.

As the public becomes accustomed to what is being done in the way of prostheses for the face, requests have come for restorations hitherto considered not only beyond the scope of plastic surgery, but also beyond the scope of prosthetics. One's first impulse is to tell such a patient that the restoration asked for is not being done. But the plastic surgeon who does prosthetic work must realize that his office or clinic is the court of last resort for such patients and, if he had no restoration to offer, the patient may become convinced that his case is hopeless. He is besieged by requests not only to restore missing parts of the face, but also to restore other parts such as the breasts, the hand, the buttocks, the penis and the calf of the leg.

Small prostheses for the face can be made of solid rubber or hollow rubber, molded by relatively simple techniques. Prostheses for the breast, the buttocks and the calf of the leg, if made by the same technique, would be heavy, bulky, unwieldy and relatively non-resilient. They should be light enough in weight so that a relatively small amount of adhesive will keep them in place, or so that no adhesive at all is necessary. They should also, unlike facial prostheses, have the rebound elasticity characteristic of the organ which they replace. For instance, when the artificial ear is bent forward and released, it should spring back into place immediately, as does an ordinary ear. Likewise, the artificial calf of the leg when pressed with the finger, should rebound at the rate normal for calf tissues.

There is no doubt that the atomic age and bacteriologic warfare will bring new and maliciously clever methods of destruction to light in our generation. This is to be normally expected. World War II produced many more facial and body mutilations than resulted from the First World War. With the next struggle, civilian populations will be even more intimately involved, and, as at Hiroshima, many thousands will suddenly be left hideously deformed.

Plastic surgical procedures designed to correct disfigurements have more or less kept pace, limping forward, as the needs of each new problem were evident, to develop new plastic surgical techniques to meet them. Even today it has been found inadvisable to operate on all mutilating injuries. Frequently it is better to replace missing parts of the face and body with lifelike substitutes than to attempt reconstruction with living tissue. Some of the reasons for declining to attempt surgical tissue alterations are intercurrent disease, the fragility and atrophy of the host tissue, and the natural debility of age. The new atomic and bacteriologic warfare will beyond doubt increase the first 2 categories of facial and body deformities which will be beyond the restorative power of

plastic surgery. For the atrophy, the telangiectasis, the keloidal change and the precancerous condition of atom-bomb exposed tissue forbids surgical modelling. Nor can surgical sculpture be tolerated by tissues whose hematopoietic system is deranged.

All this will lead the medical profession to a more serious consideration of the prosthetic art. Prosthetic restoration techniques have until recently been an orphan child of the medical profession—one might almost say a bastard child of medicine. Restorative cases were grudgingly admired for the moment, but given neither permanent nor recognized places in the clinics or medical schools. And cases beyond the power of plastic surgery have only grudgingly in the past been assigned for prosthetic correction. It seems that only by the "bloody" correction could a patient be really benefited according to most members of the healing profession.

Despite the almost "do-nothing" attitude of medicine as a whole, some men have tried through the ages to replace missing parts of the face and body with substitutes, rather than attempt reconstruction with living tissue.

Some of the substitute materials, notably latex rubber² and some of the newer polymerized synthetic resins, such as polyvinyl butyral, have already proven their worth as restorative substances. The surgeon is the first to confess that reconstructive operations, such as that of the total ear, often at best carry the probability that the esthetic result of a whole operative series will be only fair. By prosthetic techniques, though, an ear of latex or of vinyl resin can be made to match its mate with accuracy, both as to color and translucence, with lifelike elasticity, and certainly with excellent sculptural details. Such an ear, applied with a perspiration resistant cement, can be produced without pain, without hospitalization or loss of the patient's working time. It is easier on the patient, the doctor and Society. After a few recent wars,

with the subsidization by government, rehabilitation with prostheses among both military and civilian population is an improved and broadened art. Using the most suitable of the new synthetic compounds as fast as they are developed, the modern prosthetic expert is keeping pace with advancements in industrial fields.

All this is being accomplished by a few medical men who form an inner clique of men interested in helping the cases heretofore considered beyond ordinary help. Men unconsciously dedicating themselves to help the poor patients who heretofore were transferred from department to department, from clinic to clinic, with nothing offered, to conceal if not correct, their revolting faces, and make life more endurable.

To help such people, however, requires more than the ordinary knowledge held by possessors of an M.D. degree. Men who seek to restore these deformities must have some knowledge of art, whether it be formally acquired or not. They must have mechanical ingenuity; they must have a practical ability in chemistry—they must be improvisers, experimenters, and true practitioners of medical art. They must have obstinancy and courage—courage enough to carry through and produce previously impossible-to-make artistic restorations, courage to overcome the obstacles intrinsic to each unusual case as it presents itself, and above all, courage enough for the patient, too.

Fortunately, there are such men in medicine. It is a credit to our profession that there are men willing to undertake this unprofitable (yes, unprofitable), exciting, and often exasperating work. Because of these true physicians, new names are creeping into medicine. Insinuating into medical terminology are the names of vinyl resins, synthetic latices, neoprene dispersions, the methacrylates, new monomers and plasticizing agents.

New products of manufacture now rest in the doctor's laboratory. Colored lacquers, tints and dyes from all industry are now combined to make artificial resto-

tations the important adjuncts of surgical—and medical—practice they deserve to be. And the patient with inoperable lupus of the face, the patient with hideous tertiary syphilis, even unresponsive to medication, is helped.

Special equipment is now visible in the doctor's laboratory. Heaters, ovens, mixing equipment, homogenizers, grinders, polishers, caulking guns, are borrowed from industry to help the deformed. This is as it should be.

There are definite satisfactions which come to one who undertakes this sometimes heart-breaking work. Among them is the comradeship which develops between men of various professions for a common cause. Once the purpose of the work is explained, the coöperation from engineers, chemists and other researchers in industry is astonishing.

But there are other satisfactions. They might be called secret satisfactions. All doctors find time to think of their work at odd moments, when they are driving, smoking, drinking coffee with friends. They think of their work, naturally; of provoking cases, of puzzling reactions. What does the doctor think of who has found himself captivated by the restorative art? What are some of his basic problems? He finds that present problems are linked to the latest discoveries of industrial chemistry, and finds fascination in attempting to adapt these newer techniques to his own art for the benefit of his patients. He finds that his art is retrogressively connected with the art problems of the Renaissance. He cannot reconstruct artistically without a knowledge of the rules of proportion. For these he cannot depend, strangely enough, on modern textbooks; he must go back and examine the observations of Leonardo da Vinci on anatomy, and for the laws of optics as they apply to shadow, to Albrecht Dürer for some rules of facial harmony. He must investigate Brunelleschi and Botticelli, who, with Dürer and Leonardo, helped to develop an artistic naturalism. It is clear that today the medical restora-

tive artists are a small circle of kindred spirits, more interested in things than in idle hypothesizing, and more interested in experimental inquiry than in hackneyed medical and surgical opinion.

The modern practitioner of restorative art finds himself wondering upon the nature of color. He finds himself reading the theories of color, practically and philosophically. The theories of color of Des Cartes, of Hooke, of Bacon, become important. In the time of Newton, Grimaldi showed that very narrow beams of light, ordinarily travelling in straight lines (page Einstein!) are bent at the sharp edges of obstacles, so that the shadows are larger than they really should be, and fringes of color are formed. Newton showed that the bending is increased by passing the light through a narrow slit. All these behaviors of light, of shadow, of color, occupy the attention of the modern restorative artist. Thus, ultra-modern as is his work, he is united in

spirit with the artists and scientists of all ages.

He finds himself posing questions which are strange to modern medicine. Why are fingernails, the cornea and tooth porcelain fluorescent to ultraviolet light? If artificial teeth, artificial eyes and artificial fingernails possess fluorescence by artificially adding coal-tar extracts to them, why are they more lifelike? Why is blue sometimes discernible in Negro skin? How much of skin color is due to pigment, how much to transmitted color from the flesh below? How fluorescent is sebum? Is perspiration fluorescent? What is the mechanism of scoliosis after breast amputation?

These are the questions posed to modern practitioners of the restorative art. These problems, to the average doctor, seem annoying. To those who do this work, these problems are exasperating—but delightful.

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BOOK REVIEWS AND NOTICES

MEDICAL ADDENDA. RELATED ESSAYS ON MEDICINE AND THE CHANGING ORDER. By NEW YORK ACADEMY OF MEDICINE COMMITTEE. Pp. 156. New York: Commonwealth Fund, 1947. Price, \$1.75

THESE essays constitute a more complete exposition of the modern trends in the practice of medicine as visualized by the Committee on Medicine and the Changing Order of the New York Academy of Medicine. The names of the contributors, J. A. Miller, L. Hamman, Mary A. Cannon, Winifred W. Arrington, H. A. Rusk and E. P. Boas, indicate the high quality of the material presented. The book should be on the desk of everyone interested in medical practice.

T. M.

THE SKIN MANIFESTATIONS OF INTERNAL DISORDERS (DERMADROMES). By KURT WIENER, M.D., Dermatologist, Mt. Sinai, Deaconess, and St. Michael's Hosps., Milwaukee. Pp. 690; 400 ills.; 6 color plates. St. Louis: C. V. Mosby, 1947. Price, \$12.50.

THIS is a satisfactory book which fills a long-felt need for the general practitioner, the internist and the dermatologist. It should go far to dispel the "superficial" nature of dermatology and to place this branch of medicine in its proper position as an integrated part of a whole.

While there have been previous attempts to compile the dermatologic aspects of internal diseases, the efforts have been somewhat sketchy and incomplete, and are now out-of-date. Here the author has produced in a reasonably-sized volume a comprehensive, fairly complete, discussion of "dermadromes"—a word the author coined to represent the cutaneous part of a syndrome. The material is presented in sufficient detail, as a rule, to be adequate for the particular medical public for whom the volume is intended.

A wide range of subjects is covered. In 43 chapters, are considered: the Dermadromes of Systemic Infections; of Helminthic Diseases; of Tuberculosis; Dermatoses with Claimed but Still Controversial Tuberculous

Etiology; Leprosy; Dermadromes of Intoxications; of Disorders of the Circulation; Kidneys; Endocrine Glands; including also Puberty, Menstruation; Pregnancy; Childbirth and the Puerperium; the Skin of the Newborn; Menopause, and Miscellaneous Dermatoses with Endocrine Background; Ageing; Metabolic Disorders; Disorders of the Blood and Blood Forming Organs; Internal Cancer; Disorders of the Nervous System; Gastrointestinal Tract; Liver and Pancreas, and Respiratory Tract.

The material is well illustrated by clinical photographs from a variety of sources (no one man's personal experience could encompass all the data presented). Bibliographic references are given as footnotes on the same page as the material to which they refer, a method Wiener prefers not only as a matter of fairness to the author quoted, but also to induce the reader to look up some of the original sources himself. This is apparently becoming good American procedure in medical book publication, one of which the reviewer approves.

The reader will understand that the criticisms which follow are intended to be illustrative and not to detract materially from the value of the book as a whole. While its general format is excellent, color-plates, costly and superficially attractive, are in a state of technical development which seldom justifies their wide use instead of black and white illustrations. When added to this a number of unrelated color-pictures are put on one plate, somewhat removed from the text, they become like so much wall paper—this is the situation in Wiener's book. There are few typographical errors. A generally better correlation of plates and pictures with the text, more widely used terminology, as well as uniformity of spelling, would strengthen future editions. At first glance, the reviewer is struck by the numerous citations of foreign (viz. German) references (a reflection of the author's medical background) but a more critical study of the text reveals that very little in the American literature is omitted. The only fair conclusion is that the author is admirably suited

to his task because his training and experience have given him a grasp of the American, as well as European thought.

The use of eponyms is over done. The index is far from complete. Since the quality of the index makes or mars the usefulness of a book intended chiefly for reference, this is especially unfortunate. It is possible to make up an arbitrary list of subjects which are covered in the text but cannot be found in the index.

Moreover, an excellent feature, placed at the end of the book, is the group of tables on the Acute Exanthems; Diffuse Pigmentations; Diffuse Yellow Pigmentations; Hirsutism; The Skin in Relation to Age; The Hemorrhagic Diseases and Pruritus. They serve as ready reference and it is hoped that many more of them will be added in future editions.

The omission of a presentation of Syphilis is regretted. At least a photographic representation of the cutaneous aspects of Syphilis, and some differential tables would be helpful.

Allergy is becoming more and more important in certain aspects of dermatology, especially so in the case of food allergy. That there is no real presentation of allergy in such a book as this is a serious omission. Among some of the items which might be expanded are: Periarthritis Nodosa and its relationship to drug allergy (Sulfonamide); a discussion on "Stevens-Johnson's Syndrome;" Sporotrichosis as a systemic disease; Granuloma Inguinale as a systemic disease; a wider discussion of Telangiectasia; Symmetrical Erythema of the palms; more discussion of Panniculitis; more up-to-date Leprosy discussion; Premenstrual tension; Protein Metabolism, Water Balance, and Cutaneous Disorders.

The reviewer has tried to be as critical as possible; but aside from easily-corrected shortcomings, he has nothing but praise for a volume which fills the great need for better understanding between the Dermatologist and his colleagues.

H. B.

THE ENGRAMMES OF PSYCHIATRY. By J. M. NIELSEN, M.D., F.A.C.P., Assoc. Clinical Prof. of Neurology and Psychiatry, Univ. of Southern California, and GEORGE N. THOMPSON, M.D., Formerly Chief of Psychiatric Service, Los Angeles County Gen-

eral Hosp. Pp. 509; 28 ills. Charles C. Thomas, 1947. Price, \$6.75.

In this 500 page description of the neural patterns of normal and abnormal thought the physician is told that he can "move in an orderly manner and accurately—in a psychiatry which is concrete and factual" and which is founded on the basic sciences of anatomy and physiology.

The authors have made an earnest, conscientious and interesting effort to find what neural patterns underly conation, instincts, will and the personality. The definitions are pretty much their own. A typical statement is that "psychosomatic" should be changed to "brain-somatic," as it is the brain and not the mind which sends messages to the soma.

The psychoneuroses are covered in 27 pages (psychopathic personality in 40). The psychoses are introduced by schizophrenia. In this illness the commonest upsesting factor is given as "infectious illness;" the pathophysiology depends on "engrammes located in the diencephalon" which are disorganized; the disease later spreads to the cortex; the symptomatology is to a considerable extent physical; the treatment is shock therapy followed by re-education. In the chapter on Treatment in Psychiatry, about half of the procedures are given as physical and half as psychotherapy.

The reader interested in psychoanalysis will turn to another book.

E. B.

MEDICAL DISORDERS OF THE LOCOMOTOR SYSTEM, INCLUDING THE RHEUMATIC DISEASES. By ERNEST FLETCHER, M.A., M.D., (Cantab.), M.R.C.P., of the Royal Free Hosp., etc. Pp. 625; 262 ills. Balt. and London: Williams & Wilkins, 1947. Price, \$11.00.

In this book, Dr. Fletcher and 9 contributors attempt "to bring under one cover the available information on the subject of the medical locomotor disorders." They exclude the cerebrospinal system.

Following a review of the anatomy of the joints, muscles and bones, 4 chapters describe rheumatic fever and chorea, 12 chapters deal exhaustively with the more common arthritides and 2 chapters contain brief descriptions of many of the rarer affections of the locomotor system. Among others, one notes

single chapters on examination of the patient, joint physiology, fibrositis, medical diseases of bone, focal infection, radiology, gout, sciatica, and physical therapy.

The material is sometimes more abundant than well organized; *e. g.*, under "Treatment of Rheumatoid Arthritis" a discussion of 10 drugs is followed by a page or so on "Exercises for the Arthritic Patient" which is, in turn, followed by a discussion of 7 more drugs. Reiter's Arthritis is inadequately described on page 287, and fully described on page 406, although the latter is not indexed. For some reason scleroderma, dermatomyositis and myasthenia gravis are dismissed in a few words but space is found for Paroxysmal Proetalgia, although it seems hard to identify the rectum as part of the locomotor system.

The book is well bound and illustrated. Its great mass of facts are valuable from the historic, scientific and clinical aspects of rheumatism. It will be particularly useful as a reference book to the internist who is already interested in rheumatism.

J. L.

HISTOPATHOLOGY OF THE EAR, NOSE AND THROAT. By ANDREW A. EGGSTON, B.S., M.D., Director of Laboratories, Manhattan Eye, Ear and Throat Hosp., and DOROTHY WOLFF, A.B., M.A., Ph.D., Research Investigator Endaural Hosp., New York. Pp. 1080; 505 ills; 28 color plates. Balt.: Williams & Wilkins, 1947. Price, \$18.00.

ALTHOUGH the book will generally speaking be of great value both to the otorhinolaryngologist and the pathologist, its title is somewhat misleading. Histopathology as such is the weak point of the volume. The microscopic appearance of the various lesions described is covered rather briefly for a work of this size, and such descriptions as do appear tend to be poorly presented and buried under a wealth of other material.

The interest of the authors seems to center about anatomy, gross and microscopic, embryology, and physiology. A separate chapter is devoted to each of these subjects as it applies individually to ear, nose, and pharynx. These reviews are at once clear and comprehensive. Particularly good are the chapters on comparative anatomy in which the development of the respective

organ is traced from its beginning in *Amphioxus* and the lower vertebrates.

Clinical correlation is foremost in the chapters devoted to pathology. Especially emphasized are gross pathology as seen by the clinician, routes of spread, in the case of infection and tumors, and prognosis. From this point of view the book is of equal or greater value to the clinician than to the specialist in pathology. Of special value to the pathologist are several sections on the technique of dissection of the regions discussed.

The volume is greatly enhanced by extensive references at the end of every chapter, and by excellent and numerous illustrations; photographs, line drawings and color plates. The historical background of many diseases is presented in great detail.

A. R.

CINEPLASTY. By HENRY H. KESSLER, M.D., Ph.D., Foreword by Ross T. McINTIRE, Vice-Admiral (M.C.), U.S.N. Pp. 210; 314 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

THIS book is written by the one in this country who has probably had the most experience and interest in rehabilitation surgery. The intricacies of cineplasty are not too well known even by the best of orthopedic surgeons and Dr. Kessler stands out as the one willing to devote his time and effort to this branch of rehabilitation. He reviews the mechanics of the hands and details the various types of mechanical prostheses and discusses their advantages and disadvantages. The physiology and anatomy of the muscles of the upper extremities are discussed with respect to their function as motors. His chapter on Surgical Technique discusses the possibility of forming useful motors from remaining muscles. The various procedures are described in detail, both for below-the-elbow amputations and for those above the elbow. Cineplastic prostheses are described and illustrated. Finally, considerable emphasis is placed upon the rehabilitation of the amputee in helping him to regain his self-confidence and to return to a useful life. Dr. Kessler's book is of particular value to those interested in rehabilitation as well as to orthopedic surgeons. It is probable such cases will be referred by those who have read this book to men who have had experi-

ence in this type of work. The impression gained by the reader is that this is not a type of surgery to be attempted by the inexperienced.

The illustrations, taken from Dr. Kessler's own cases, are excellent.

L. F.

THE MEDICAL WRITINGS OF ANONYMOUS LONDINENSIS. By W. H. S. JONES, Litt. D., F. B. A. Pp. 168. Cambridge, at the University Press. New York: The Macmillan Company, 1947. Price, \$2.75.

THIS is the first English translation and critical edition of a British Museum papyrus (dating probably from the second century A. D.) that was discovered in 1891, and the *editio princeps* of which was brought out in Germany in 1893. A German translation was published in 1896.

The papyrus is a copy made by a medical student, W. H. S. Jones conjectures, of lecture notes also made by a medical student, perhaps on several lectures. The work falls into three distinct parts: (1) definitions; (2) descriptions of the views on pathology of predecessors and contemporaries of Hippocrates; (3) a history of physiology after 300 B. C. from Herophilus to Alexander Philalethes. The second part is of particular importance as representing more fully than hitherto the non-extant historical work of the Greek physician Menon, a pupil of Aristotle. Indeed, the passage therein describing the views of Hippocrates is coming to be accepted as one of only two reliable testimonies for the doctrine of the historical Hippocrates.

Text and translation are printed on facing pages. An introduction records the critical history of the text since 1893, describes the contents, and discusses the problems of authorship and sources. Additional notes, footnotes, a bibliography, and an index of *notabilia* complete the scholar's apparatus. An excursus, there are a note on the nature of Greek thought and another on the nature of Greek Medicine.

It is good to have this important text made available in English by a scholar so singularly well-equipped to elucidate its complex fabric and meaning.

W. McD.

OSTEOTOMY OF THE LONG BONES. By HENRY MILCH, M.D., Consulting Orthopaedist, Maimonides Hospital. Pp. 294;

181 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

AN accepted method of effecting an osteotomy of a long bone 25 years ago was by a thrust of a chisel through the skin to the underlying bone, a twist of the handle to bring the blade transverse to axis of the bone and a whack by a mallet to produce the dissolution of the bone. The alignment of the fragments was judged mainly by external appearances. The duration of immobilization for union of the osteotomy was by "rule of thumb." With the coördination of the knowledge of pathology, physiology of bone, roentgen study and improved surgical technique, the method of effecting an osteotomy has become more complex; but a greater range of application has been attained and a uniformity of better results.

Dr. Milch has written a book which correlates the many advances in the analysis of deformities of the long bones and their mechanical correction. He frequently reveals the advantage of using a mathematical equation to obtain the desired mechanical result. His abduction osteometer is an ingenious apparatus for determining the optimum angle of correction for hip joint deformity. In a logical manner he considers the 4 directions in which displacement may occur when an osteotomized long bone deviates from its mechanical axis. He considers 4 types of osteotomy that produce a monoaxial displacement in each of the 4 directions: (1) lineal, with displacement longitudinally for shortening or lengthening; (2) torsional, for correction of rotation deformities; (3) transpositional, with displacement laterally so that the axis remains parallel to the original axis; (4) angulated, with the distal fragment angulated about any point along the axis.

This book sticks to the subject. It is a manual on the mechanics of osteotomy of the long bones. It does not deviate into diagnosis or operative technique. It is an excellent source book for the orthopaedic surgeon.

J. N.

NEUROPATHOLOGY, ITS CLINICOPATHOLOGIC ASPECTS. By I. MARK SCHEINKER, M.D. Foreword by TRACY J. PUTNAM, M.D. Pp. 306; 208 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

THIS book is highly recommended as valuable both to the neurologist and the path-

ologist. Although the volume is brief, the included subjects are discussed fully and to the point. The style achieves easy reading and the subject matter is clearly and concisely presented. The chapters are well arranged, in logical sequence. The principal topics discussed are vascular diseases, demyelinating diseases, neurosyphilis, inflammatory diseases, myopathies, syringomyelia, cerebellar disorders, and degenerative diseases. Conspicuously absent are such important topics as tumors, congenital malformations, and intoxications; and this, in the opinion of the reviewer, is the principal adverse criticism of the book.

Concise historical reviews are given for each disease. The pathologist will appreciate the lucid descriptions of both gross and microscopic findings. The clear and well-chosen illustrations are helpful in supplementing the verbal descriptions. The clinician will be interested in the excellent clinical descriptions of the included diseases, and in the close clinicopathological correlation. The bizarre terms that clutter many works on neuropathology have been largely replaced by those more familiar to the average physician. An unusually good presentation of the various encephalitides, and of fungus diseases of the central nervous system is included. An extensive bibliography is provided.

A. R.

DIAGNOSTIC BACTERIOLOGY. By ISABELLE GILBERT SCHAUB, A.B., Instructor in Bacteriology, Johns Hopkins Univ., and

M. KATHLEEN FOLEY, A.B., Instructor in Bacteriology, College of Notre Dame of Maryland. 3d ed. Pp. 532. St. Louis: C. V. Mosby, 1947. Price, \$4.50.

This is a technique book of determinative bacteriology, divided into 3 principal sections: (1) Bacteriological Diagnosis, (2) Serological Diagnosis, and (3) Media, Stains and Staining Technique, etc. As in previous editions, methods for the isolation and identification of bacteria are given clearly and concisely step by step and day by day. Included with each group of organisms are numerous tables showing the differential procedures to be followed. In this edition there are new tables for the intestinal Gram-negative bacilli and the aerobic streptococci. A new Chapter 1 concerned with elements of technique has been added. This edition has been expanded also to include explanatory and theoretical discussions of technique. The left-hand pages again are blank for student's notes.

As is the case with most technique books concerned with such an inexact science as diagnostic bacteriology, the methods recommended will not be approved by all. The authors have had wide experience in the isolation and identification of pathogenic bacteria, however, and the techniques in general are sound and practical. Consequently the book should be especially useful for technicians and medical students and should be a valuable addition to any library of clinical bacteriology.

R. N.

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ORIGINAL ARTICLES

SPECIAL METHODS FOR THE DIAGNOSIS OF TUMORS IN THE LABORATORY

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NEW YORK, NEW YORK

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New York Hospital)

It should be made quite clear at the outset of this paper that there is no royal road to the diagnosis of tumors in the laboratory; whatever methods be used to differentiate oneneoplasm from another the diagnosis still depends upon the training and experience of the observer. Tumors have definite physiognomies and you all became more or less familiar with these in the 2nd year classroom, when you studied carefully selected sections or specimens. Most of you have, I fear, stored this somewhat painfully acquired knowledge on the top shelf and, should you take it down and look it over, you would find that it had accumulated a lot of cobwebs.

The diagnosis of tumors is largely a matter of seeing many examples of them and, just as one becomes acquainted with people, getting to know them without having to turn on the high-powered lens and search for details. There is no stain that will automatically issue a diagnosis and there are few rules in the recognition of tumors that do not have their exceptions. A few weeks of studying sections in a laboratory of surgical pathology is worth many months of reading in text-

books. Some tumors have many variants or differing types of growth, no one type may be considered to be the inflexible prototype of that particular neoplasm.

Granted that the pathologist has the necessary background, however, there are many methods of going about the securing of a diagnosis, some of them partial or indicative and useful for screening out obvious cases, others ancillary to the routine, but in the end the paraffin section, properly stained, is the last court of appeals.

In presenting this subject it would be well to begin with the simpler methods and progress to the more complicated procedures. Simple methods are calculated to cause the least disturbance to the patient, physician, surgeon and pathologist. Those which are more complicated often produce discomfort for the patient and make demands upon the skill and experience of the physicians involved.

SMEARS. The recent work of Papanicolaou has given great impetus to the diagnosis of malignant growths in smears. He began by studying the cytologic changes in the vaginal epithelium in vari-

* Delivered at the University of Buffalo, School of Medicine, Centennial Symposium on Cancer, October 1, 1946.

ous phases of the menstrual cycle and under varying conditions of hormonal stimulation. While carrying out his investigations he noted that cells of malignant tumors were encountered in some of the smears. As these were readily recognized he accordingly expanded his technique to facilitate this form of diagnosis. At first a side line in his investigation, this very important feature has become a main line and he has devised methods for examining not only vaginal smears, but also material obtained directly by intra-uterine aspiration. Thus he was enabled to narrow down his sources of pathologic cells and to determine definitely that a given tumor was intrauterine and not located in the cervix uteri.

It was not long before he branched out and began examining smears of other fluids and secretions. It was found that the urine from a bladder which was the site of carcinoma might contain carcinomatous elements and that these could be concentrated by centrifugation and thus readily identified. A noteworthy example of the practical value of this method was the discovery of cells from a carcinoma in the urine of a bladder which, on cystoscopic examination, showed no carcinoma. Investigation revealed a fairly large diverticulum and, at operation, a carcinoma was found tucked away in the fundus of this, safely hidden from the visual field of the cystoscope.

It was evident from the success of these 2 lines of experimentation that the method might be extended to an examination of aspirated fluids from other hollow viscera such as the stomach and the pulmonary tree. Accordingly these were investigated and it soon became evident that the method was of distinct value in connection with the examination of smears of gastric contents and of sputum or bronchial washings, although diagnosis was found to be more difficult in this case than in that of the genitourinary system.

The success of the method depends upon the fact that carcinomas tend to break

down superficially and to cast off cells into the fluid that bathes them. If the malignant tumor be intramural and does not desquamate into the cavity of the organ, the method will, of course, not succeed. This would be true of leiomyoma of the wall of a viscus, as well as of leiomyosarcoma—unless that tumor had eroded its way through the lining mucosa.

There is nothing miraculous about the technique; it depends simply upon 2 factors: carcinomatous cells must be present and the pathologist who searches for them must have had sufficient experience to be able to recognize them when he sees them. The procedure, then, should not be entrusted to anyone who is unfamiliar with cancerous elements, but should be carried out by an experienced pathologist. The qualified pathologist is usually well acquainted with the appearance of carcinomatous or sarcomatous cells; they are usually of abnormal size, irregular outline and poor histologic differentiation; they are generally very variable in diameter; they present nuclei that are hyperchromatic and stain intensely, often possessing very large and prominent nucleoli. They may show normal, or very abnormal mitotic figures. Thus it becomes easy for an experienced observer to recognize them and report their presence in a given smear.

The method has few drawbacks. A carcinoma of any size will usually cast off cells or clumps of cells which may be found after a few minutes of searching. If the pathologist is very much busied with routine, it is not often feasible for him to spend $\frac{1}{2}$ hour or so in searching through a smear poor in cellular elements. A few such smears would occupy an 8 hour day! It is found, however, that if carcinoma is present, its cells are usually so striking in their appearance that they are readily found after a few minutes.

One needs very little equipment for carrying out such examinations. The fluid is either smeared-out as it comes to the laboratory, without concentration, or if it be very dilute (like urine or bronchial

washings) it may be necessary to concentrate it by sedimentation. The smears are allowed to dry on microscopic slides and are then fixed in equal amounts of ether and alcohol. They are then stained by some good method like the trichrome stain of Masson. The cellular details as revealed by this are excellent, and one gains very beautiful pictures of ciliated cells from normal bronchial mucosa, the cilia bright red and the cytoplasm grayish green. The carcinomatous elements stand out by their lack of differentiation and their rather drab color reaction. When urine is to be examined, Papanicolaou and Marshall have found it advisable to mix about 40 cc. of this in a test-tube with 10 to 20 cc. of 95% alcohol. This is then centrifugated and the sediment smeared onto glass slides and fixed in alcohol and ether. It should not be forgotten that prostatic fluid is excellently adapted to examination in smears, it may be expressed by massage, smeared out and fixed in alcohol and ether, and then stained and examined for cancerous cells.

Smears from the alimentary tract are not as yet very satisfactory on account of the distortion of cells by digestion and of the presence of many foreign, though normal cells, from ingested meat and the like. For the present, direct biopsies appear to be preferable in this case.

ASPIRATION BIOPSIES. These fall into 2 categories: the material aspirated in the form of serous effusions from the pleura, pericardium or peritoneum, or the cavities of cysts or joints; and, secondly, solid matter aspirated through a needle or cannula attached to a syringe.

Serous Fluids. The examination of serous fluids for cells of malignant tumors is facilitated by allowing them to sediment by gravity in the refrigerator overnight and then centrifugating such sediments mechanically, after discarding the supernatant fluid and replacing it with a fixative such as formalin, Zenker's or another such mixture. The button is then carefully removed from the bottom of the

tube and embedded in paraffin, in which it is sectioned exactly like a piece of tissue. Such sediments may be stained as one may desire. It will be found that the pathologist must acquire a certain degree of familiarity with those cells normally present in transudates and exudates in order to recognize the abnormal elements. The chief difficulty is encountered in connection with desquamated mesothelial elements from the pleura, pericardium, or peritoneum; these may often take on very substantial proportions and mislead the pathologist. In hepatic cirrhosis there is usually a massive proliferation and desquamation of peritoneal cells, but these are remarkably uniform in size, shape and appearance, while the reverse is true in the case of neoplastic elements, which vary conspicuously in these respects. The presence of multinuclear cells and of mitotic figures in mesothelial cells is often confusing to the beginner, but as the effusion constitutes an excellent culture medium and the cells multiply and live in this much as would bacteria in broth, it is not surprising that they should take on a quasi-neoplastic appearance. When cancer is present one may find masses of neoplastic cells, sometimes attached to stromal elements, in the sediment. These groups may often be so characteristic in their appearance and arrangement that one may make a fairly accurate surmise as to the type of tumor and its primary site. The method is decried in some quarters, but this is unjust, as it has a very distinct value which should not be underestimated; in our laboratory the positive reports are better than 85% accurate, which speaks for itself.

Aspiration of Solid Neoplastic Tissue. The "needle biopsy" has enjoyed considerable vogue for a long time and consists in introducing a coarse aspirating needle, or cannula, into the depths of a suspected neoplasm and attempting to aspirate some of this into the attached syringe by exerting strong suction while, at the same time, oscillating the tip of the needle to dis-

lodge bits of tissue and facilitate their withdrawal. Oftentimes valuable fragments are thus detached and can be smeared out onto a glass slide, or even embedded in paraffin and sectioned. The method is frequently employed in our hospital for exploring the liver, even in cases where there is no suspicion of the presence of carcinoma and all that is wanted is a diagnosis of the hepatic parenchyma. Aspirated material should be fixed in an appropriate medium before it is stained. We used to employ heat, simply smearing aspirated tissue onto a slide and passing the latter through a Bunsen flame. This does not give satisfactory results, as the procedure is too drastic and the cellular details are obscured by violent coagulation. Fixation of the smear, after it is dry, in equal parts of alcohol and ether, is now our method of choice.

The aspiration biopsy has definite disadvantages: it does not give one enough tissue to afford any concrete idea of the topography of a given tumor, it merely produces its cells; it often fails entirely in the case of dense fibrous growths, where the cells refuse to become dissociated from their fellows and one obtains merely an excellent smear of blood. It has always seemed, after long experience, that it is far better to excise a bit of tissue for a biopsy and thus disturb a potentially malignant tumor as little as possible. Agitating a needle in its depths may detach cells for diagnosis, but it might also set them free into the circulation and favor metastasis. On the other hand, a piece of tumor that is cleanly excised with a sharp scalpel would seem to suffer far less cellular dissociation and thus tend to present less likelihood of metastasis. This is, of course, theoretical but I believe that it is a valid point.

Tissue Biopsy. There is little to be said here about the biopsy of tissue for diagnosis, as its excision is a self-explanatory matter and the treatment of excised tissue differs not a whit from that of a tumor which has been excised *in toto*. It

is, however, advisable to stress the necessity for the exercise on the part of the surgeon of a reasonable amount of discernment in the choice of the tissue he will excise for examination. The pathologist can diagnose only that which is in his specimen; if the surgeon cut out a piece of tissue near a tumor, rather than in it, he may miss the tumor entirely and the pathologist, failing to find any neoplastic tissue will, of necessity, report its absence. If the surgeon exposes a mammary tumor, for example, and then cuts out a piece of tissue that is hard and brawny he may get the important part of the growth; if he selects a piece that is stony-hard and which, when incised with the knife, cuts like balsa wood and leaves the edges of the incision sharply angular and not rounding-off, the matter will be simpler. If, on making the section, he notes yellowish streaks on the sectioned surface, or the yellowish "worm casts" of a comedocarcinoma, he will be even more surely producing "pay dirt" for the pathologist. A biopsy should always be as generous as is feasible, tiny bits of tissue are hard to handle in the laboratory, they are difficult to keep track of in the solutions used and they are little better than aspiration biopsies in respect to the fields of microscopic observation that they afford.

We should consider frozen sections. Surgeons should see a few of these made, if they have not already done so. They will then realize the futility of expecting a pathologist to make such sections on biopsies measurable in millimeters only, or consisting of feathery, papillary growths that fly apart after they have been frozen and cut and floated on water. All that holds a frozen section together is the tissue itself, once the ice that serves as the impregnating medium, has melted. Ice is not at all similar to paraffin or celloidin! Uterine curettings, unless very bulky and fleshy, are extremely difficult to manage on the freezing microtome; it is much better to allow the pathologist time to

run such material through in paraffin by one of the more rapid methods. It has at least once happened that I have been requested to make a frozen section of a bony tumor! A little thought should convince the operator that bone requires decalcification before it can be cut and that decalcification is a matter of days.

Special Stains in Diagnosis. The average American pathologist is a man who is used to thinking in terms of red and blue; the nuclei of the cells in a section stained by the usual hematoxylin-eosin, or eosin-methylene blue methods are blue, everything else is red. This is all very well for the diagnosis of simple, "run of the mine" sections from familiar tumors; but when a growth is complicated, this simple and overworked method falls down lamentably. It is strange that so many pathologists depend upon it exclusively and, when they send sections of tumors for consultative diagnosis (tumors that are thus admittedly tricky), send only those stained by this conventional technique. The advantage of a colored map of, say, the State of New York, with the counties in contrasting colors, is the fact that it is much more rapidly understood than one in black-and-white; this is no less true of microscopic sections in which various tissues assume various colors in the slightly more complicated stains, but only 2 in hematoxylin and eosin.

Thus a good polychrome stain is vastly superior because it affords immediate orientation as to the various components of the tissue to be examined and time is not lost in trying to identify these elements by morphology alone. As connective tissue fibers are stained green or blue in Masson sections, while muscle is red and neural sheaths golden yellow, one wastes no time in identifying them. Thus a fibroma would be mainly green and a muscular tumor mainly red, erythrocytes would be orange, fibrin vermillion, keratin orange and mucinous tissue green.

There is no facile formula for the diagnosis of a malignant as opposed to a non-

malignant tumor insofar as specific stains are concerned; it is purely a matter of morphology and familiarity with the criteria already adumbrated elsewhere in this paper. When it comes to identifying the source of a tumor, however, the matter is different. We have at our disposal an enormous number of stains for the demonstration of specific chemical substances and histologic elements which enable a reasonably versatile pathologist to come very close to an accurate determination of the tissue-of-origin of a given growth and this may often be of great importance as it may indicate wide differences in the prognosis.

Let us suppose that a tumor is full of granules of a brown pigment: is this melanin, or is it not? If it be melanin, the prognosis may be very bad. Recourse to Perl's stain, which is merely the old Prussian blue reaction for free iron, will at once determine whether the pigment is hemosiderin. This is a common by-product of degenerated hemorrhage and means little in the prognosis. If the granules turn greenish blue the pigment is hemosiderin, if they remain brown it is something else. Impregnation with appropriate solutions of silver salts will turn melanin black, even in its colorless, or premelanin phase.

The prognosis of mammary carcinoma is said to be better if mucous deposits are found within the cells, or in the stroma. This substance is readily recognizable without special stains in the latter case, but when it is included in the cellular cytoplasm it escapes notice in ordinary sections. In those stained with Meyer's nuccicarmine,* however, each droplet of mucus will come out bright carmine and one may readily determine the general prevalence of mucus in the section and render an accordingly more favorable prognosis. This has worked out well in our laboratory. Another carmine stain is used to demonstrate glycogen and there are several tumors which contain goodly amounts of this, notably the renal celled

* The Dressbach modification has been found to be excellent (Dressbach, M., Arch. Path., 44, 391, 1947).

carcinoma of the kidney, formerly called "hypernephroma" and the rare chordoma, which develops from rests of the notochord. It is, however, seldom necessary to demonstrate glycogen in order to make a diagnosis of these neoplasms.

Rhabdomyosarcomas are fairly common and very often misdiagnosed. In establishing an iron-clad diagnosis it is desirable to demonstrate cross-striations in the cells of these growths; this is best accomplished by using Mallory's phosphotungstic acid hematoxylin, a stain that is far simpler than its rather formidable name. Cross-striations develop relatively late in the embryologic development of muscle and it is not always possible to demonstrate them in rhabdomyosarcomas; one should always endeavor to do this, however.

Leiomyosarcomas may be difficult to identify unless one employs impregnation of the reticulum with silver and demonstrates the parallel fibrils of sarcolemma that enmesh the cellular elements. These tumors sometimes resemble carcinomas, particularly when they arise in the muscle of the gastric cardia. A trichrome stain *à la* Masson will bring out the sarcoplasm of component cells as bright red, polar accumulations, thus differentiating them from epithelium or fibroblasts.

One of the knottiest problems in the diagnosis of tumors exists in connection with the group of lymphosarcomas and Hodgkin's granuloma. Here it is imperative to employ Zenker fixation and the Giemsa stain, which has proved its worth in connection with lymphoid tissue. The eosinophils which constitute one-third of the "Hodgkin's trilogy" are brought out in bold relief by this method, the lymphoid elements are more specifically stained and their basophilic qualities accentuated. Thus the latter can be differentiated from the paler reticulum cells.

Those of us who put store in separating the tumors of the reticuloendothelium (or "retothelium," as Roulet calls it) from the other elements of lymphoid tissue will find silver impregnation invaluable in

clinching the diagnosis. The fibrils of reticulum penetrate among and around the cells of the tumor and thus differentiate it from a carcinoma, which it sometimes resembles. In carcinomas the reticulum forms a basal membrane about groups of epithelial cells and does not penetrate into their complexes at all conspicuously.

The tumors of the nervous system, whether central or peripheral, have only comparatively recently been placed upon a scientifically devised basis by means of recourse to silver impregnations of various sorts, depending principally upon the methods of Ramon y Cajal, who employed silver nitrate, and on those of Bielchowsky, who used a double salt of silver, the diammino hydroxide. A large number of methods were derived from these by del Rio Hortega, Bailey, Penfield, Globus and many other investigators. By using these procedures it is possible to split up the large groups of "gliomas" into a number of subsidiary types each of which carries a slightly different prognosis. The old diagnosis of "glioma" was unpredictable, the modern classification ranges from the non-malignant astrocytomas and oligodendrogliomas to the very malignant glioblastoma multiforme, which is unfortunately among the commonest of cerebral tumors. Once a pathologist has familiarized himself with these forms of neurogenous tumor, the invariable use of silver impregnations becomes relatively unnecessary; a good Masson trichome stain is usually sufficient to present evidence which may be accurately evaluated and diagnosed, although it is usually followed up by silver impregnations (which take more time to prepare) as a confirmatory measure.

Tissue Cultures. Stout and his collaborator Murray have recently shown the advantages of growing tumors in tissue cultures; this is a very specialized technique which is delicate and rather capricious until mastered. It began with Harrison's experiments with the explanted amphibian nerves and grew under the direction of Burrows, Carrel, Ebling and

others until it attained universal attention and was also extensively used in England and Germany. Stout and Murray have been explanting small pieces of human tumors into appropriate media and have studied the individual cells as they grew out from the explant. In this way they have been able to observe differences between fibroblasts and lemmoblasts and to determine that a neurofibroma is really a rather scirrhous form of neurilemmoma, most familiar to you as the so-called "acoustic neurinoma." Their experiments are not confined to neurogenous tumors, as they have subjected many types of growth to test in tissue cultures.

Akin to the tissue culture is the study of tumors explanted into the anterior chamber of the eyes of experimental animals. Greene has done very valuable work along this line. While the transplantation of tumors from one species to another usually fails if the explant is placed in subcutaneous tissue, muscle, or a body cavity, the anterior chamber of the eye appears to be incapable of producing antibodies that destroy such explants in these other situations. Thus the growth of a tumor may be studied through the slit-lamp microscope as it progresses in the transparent organ. It takes these explants a long time to become accustomed to their new habitat and to grow there, but once they begin to grow they make rapid progress. Both the tissue culture and the ocular culture are more suited to experimental observation than to diagnosis, but it is only by experiment that we get to know something about these tumors.

Laboratory Procedures in Diagnosis. As certain neoplasms cause changes in the biochemistry of the body, this fact has been employed as a diagnostic adjuvant in the case of such growths. Choriocarcinoma will increase the chorionic gonadotropin (formerly called "prolan") of the blood and urine, so that the patient reacts to its presence as would a pregnant woman

to that of a placenta. Carcinoma of the prostate is accompanied by increase in the acid phosphatase content of the blood, particularly when there has been widespread metastasis. Bence-Jones proteins appear in the urine of patients with multiple myeloma of bone, as well as in the presence of some other tumors. Desoxycorticosterones are increased in the case of cortical adenomas of the suprarenal. All these phenomena, when proved, are merely indicative of the nature of a tumor; its final diagnosis will nevertheless still depend upon its appearance under the microscope.

For a while it was fashionable to employ certain fish to serve as indicators of increased gonadotropin in the urine. A little of this liquid from a pregnant woman, or a patient suffering from choriocarcinoma or malignant melanoma, when added to water in which these fish were kept would cause them to react characteristically. The male of the German minnow known as the "Elritzer" would take on gorgeous colors along his belly, the female bitterling would protrude her ovipositor, the female African frog would immediately lay eggs if gonadotropic material was present. Naturally the Aschheim-Zondek test is also applicable in such cases and has outlived the other methods in usefulness. But these tests are merely confirmation of the fact that there is something present in the patient which is producing gonadotropic hormones and it will not diagnose the tumor. While melanomas will bring about a positive reaction in tests for gonadotropin, it has been found that neurogenous sarcomas will also do this. There has, as yet, been no real need for the hospitals to dispense with their histopathologists, or for the latter to discard their microscopes⁵.

At one time the Gordon test for Hodgkin's disease gave some promise of diagnosing that condition without resorting to biopsies of tissue, beyond removing small fragments for injection into rabbits. In the presence of Hodgkin's disease the

rabbits would develop characteristic paralysis. Later experimentation proved that this was attributable to the presence of eosinophils in the tissue and that any tissue richly infiltrated with them would provoke a positive reaction; thus the test was found to be non-specific and has been largely given up.

The functional action of tumors has been mentioned already; islet tumors of the pancreas will provoke hyperinsulinism, medullary adenoma of the suprarenal will bring about hypertension, cortical adenomas of the same gland will produce precocious sexual development and growth in children, masculinization in the female and less marked sexual changes in the male. Tumors of the parathyroid occasion changes in the calcium metabolism of the body and in the histology of the

bony skeleton. All these can be more or less accurately checked up by assays or by clinical tests, but the actual diagnosis still rests upon the outcome of histopathologic observation.

Summary. This paper, when summed up, will merely indicate that there are no "special tests" or methods for establishing the diagnosis of malignant tumors in the sense of infallible and simple procedures that are comparable with clinical pathologic assays, serologic complement fixations and the like. We are still largely dependent upon the gross and microscopic examination of the tumors, or samples of them, under the microscope. One may speak of special methods, then, only insofar as they are specialized procedures in "tissue pathology."

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FOLIC ACID THERAPY

RESULTS OF A CLINICAL STUDY*

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It is the purpose of this paper to report the results of the administration of folic acid in a variety of hemopoietic disorders. Included in this study are cases of: Addisonian pernicious anemia, tropical sprue, macrocytic anemia of unexplained origin, anemia of renal insufficiency, leukemia, idiopathic leukopenia, irradiation leukopenia associated with malignancy and leukopenic states of Addison's disease, Felty's syndrome and thiouracil intoxication. Thirty-four cases in all have been studied.

Not since the introduction of liver treatment for pernicious anemia by Minot and Murphy in 1926¹⁶ following the experimental work of Whipple²³ has so much attention been focused upon potent anti-anemic substances. The clinical and experimental significance of folic acid, particularly, has contributed to our knowledge of pernicious anemia.

Folic acid, so named by Mitchell, Snell and Williams¹⁷ because it may be extracted from spinach, is a recently recognized member of the vitamin B complex. As is so often the case, the credit for the discovery of this drug cannot be assigned to any one individual, but rather to many different groups of investigators who were working in highly diversified fields.

One of the first and most important contributions to the study of the effect of vitamin deficiency diseases upon hemopoiesis was that made by Wills, who in 1931²⁴ noted the striking effect of marmite,

a yeast extract, on the blood picture of "tropical anemia" and "pernicious anemia of pregnancy." She related the hemogram of these conditions to Addisonian pernicious anemia and stated that these diseases differed only in symptomatology. She shrewdly observed that "tropical anemia" and "pernicious anemia of pregnancy" were deficiency diseases and were corrected by an unknown substance in marmite, probably not protein in nature. She stated that "Marmite is, however, known to be a rich source of the B vitamins." Later, in 1932 Wills and Bili-moria²⁵ carried out experiments in monkeys wherein it was shown that certain vitamin B substances could correct or cure the nutritional cytopenias of these animals. In 1935, Day, Langston and Shukers⁵ were able to corroborate Wills' work on monkeys. The substance present in dried brewer's yeast which was instrumental in correcting the nutritional cytopenias of the monkey was designated vitamin M by Day, Langston and Darby⁶ in 1938.

Likewise in 1938, Stokstad and Manning,²¹ working on chicks fed all the known essentials, noted that they needed a substance present in yeast, middlings, alfalfa, or wheat bran for growth. In the next year, Hogan and Parrott^{11,12} reported similar findings and added that chicks fed a diet lacking in this unknown factor also developed a "macrocytic hyperehromic anemia." This factor, present in liver, they called vitamin B₁₂.

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From the seemingly unrelated field of bacteriology came the next important advancement, for in 1940 Snell and Peterson¹⁸ reported a substance, present in yeast and liver, which could be adsorbed on norite and eluted therefrom with ammoniacal alcohol. This substance was found to be necessary for the growth of *Lactobacillus casei* and *Streptococcus lactis*. It was called by them the "norite eluate factor."

In 1944 Hutchings, Stokstad, Bohonos and Slobodkin¹³ reported further work on the "*L. casei* factor." This substance they related to vitamin M, vitamin B₉ and the norite eluate factor.

In 1941 Mitchell, Snell and Williams¹⁷ were able to secure a substance from spinach which was essential for the growth of *Strep. lactis* and was defined by them as a growth factor for this particular organism. It was called folic acid.

The last important contribution to our knowledge of folic acid (other than clinical contributions) was its synthesis in 1945 by Angier *et al.*¹ and finally the announcement of its chemical structure by this same group in 1946.² Table 1 is a brief summary of some of the literature dealing with folic acid.

was anemia. These patients were studied as follows: After proper baseline studies, including red blood cell count, hemoglobin, white blood cell count, reticulocyte count, examination of the peripheral blood, and hematocrit studies, the patient was placed on either oral or parenteral folic acid. Thereafter daily reticulocyte counts were done. White blood cell counts, hemoglobin and red blood cell counts were done twice weekly. Subsequent to the termination of folic acid therapy the above routine was carried out for a minimum of 2 weeks if possible. The follow-up studies of Group B patients (the leukopenias) differed only in that daily white blood counts and blood smear examinations were done instead of daily reticulocyte counts. All blood counts were done with Bureau of Standards equipment. The diagnoses as listed in Tables 2 and 3 were well established on the basis of both clinical and laboratory evidence and the diagnosis of malignant disease was in each case supported by examination of suitable pathologic material.

Results. The results of administration of folic acid are summarized in Tables 2 and 3.

1. Five cases of pernicious anemia in relapse have been treated with folic acid (see Cases 1, 2, 3, 4, 5, Table 2, Chart 1). All of these cases obtained a satisfactory

TABLE 1.—FOLIC ACID GROUP OF SUBSTANCES*

I Investigators	II Date	III Name	IV Biologic activity
1. Wills and Bilimoria ²³	1932-1935	Vitamin B	Cures or prevents nutritional cytopenia in monkeys
2. Day and Langston ¹⁴	1935-1938	Vitamin M	Same as above
3. Stokstad and Manning ²¹	1938	Vitamin B	Cures chick anemia
4. Hogan and Parrott ^{11,12}	1939		
5. Snell and Peterson ¹⁸	1940	Norite eluate factor	Growth factor for <i>L. casei</i> and <i>S. lactis</i>
6. Hutchings, Stokstad, Bohonos and Slobodkin ¹³	1943-1944	<i>L. casei</i> factor	Growth factor for <i>L. casei</i> and <i>S. lactis</i> . Action similar to: vitamin B, norite eluate factor, and vitamin M
7. Mitchell, Snell and Williams ¹⁷	1941	Folic acid	A potent hemopoietic factor
8. Angier <i>et al.</i> ¹	1945-1946	Synthetic folic acid and (formula)	Similar to "natural" folic acid

* This is not intended to be a complete survey of all the substances and of all the investigators concerned with this substance.

Early in 1945 synthetic folic acid* became available in large enough quantity to enable us to treat a number of leukopenic and anemic states.

Method. The patients were divided into 2 groups, A and B. Group A patients were those in whom the primary consideration

hematologic remission in their disease following the administration of folic acid. On the average, the reticulocyte response began on the 4th to the 5th day following institution of treatment, reached a peak on the 7th or 8th day and slowly fell to pre-treatment levels within 2 weeks.

* Courtesy of Dr. S. M. Hardy of Lederle Laboratories, Inc., New York, New York.

four. 350—Adams—7* —8—
TABLE 2

TABLE 2.—GROUP A PATIENTS IN WHOM THE MAIN CONSIDERATION WAS THE RESPONSE OF THE RED BLOOD CELL COUNT AND HEMOGLOBIN TO THE ADMINISTRATION OF FOLIC ACID

Case	Diagnosis	Admission R.B.C. (mill. per c.mm.)	Discharge R.B.C. (mill. per c.mm.)	Admission Hgb. (gm. per 100 cc.)	Discharge Hgb. (gm. per 100 cc.)	Peak retic. count (%)	Expected peak retic. count with intra-muscular liver (%)	Amount of folic acid (mg. per day)	Route of administration	Total amount of folic acid (mg.)	Effect
1	Pernicious anemia	1.35	3.94	5.4	11.7	28.2	31.2	15	Intramuscularly	240	Excellent
2	Pernicious anemia	0.71	2.98	2.7	11.5	16.4	49.0	50	Orally	750	Excellent
3	Pernicious anemia	0.874	2.95	2.6	9.7	21.8	43.6	50	Orally	750	Excellent
4	Pernicious anemia	1.15	3.00	5.5	10.1	24.2	36.0	50	Orally	750	Excellent
5	Pernicious anemia	1.66	2.47	8.0	11.7	15.4	24.8	10	Orally	180	Excellent
6	Sprue	3.50	5.01	13.1	14.7	2.3	..	40	Intramuscularly	1150	Good
7	Macrocytic anemia, unknown origin	2.63	2.10	9.4	7.3	4.0	..	45	Orally	495	Poor
8	Macrocytic anemia, unknown origin	2.30	3.40	10.3	12.0	4.9	..	50	Orally	900	Questionable
9	Macrocytic anemia, unknown origin	2.37	2.20	8.8	8.5	3.4	..	10	Orally	120	Poor
10	Anemia of renal insufficiency	2.37	3.15	7.5	8.4	2.1	..	50	Orally	730	Poor
11	Anemia of renal insufficiency	1.80	1.82	6.3	6.5	6.0	..	50	Orally	750	Poor
12	Anemia of renal insufficiency	2.80	2.50	9.7	8.5	3.0	..	50	Orally	750	Poor
13	Anemia of renal insufficiency	2.69	2.73	7.3	8.2	2.5	..	20	Orally	320	Poor

TABLE 3.—GROUP B PATIENTS IN WHOM THE MAIN CONSIDERATION WAS THE RESPONSE OF THE WHITE BLOOD CELL COUNT TO THE ADMINISTRATION OF FOLIC ACID

Case	Diagnosis	Admission W.B.C.	Discharge W.B.C.	Amount of folic acid (mg. per day)	Route of administration	Total amount of folic acid (mg.)	Duration of treatment (days)	Effect
14	Addison's disease	4880	3,500	15	Orally	50	10	Poor
15	Pellagra	1790	1,350	50	Orally	700	14	Poor
16	Hyperthyroidism, thioracil agranulocytosis	1080	8,500	50	Orally	550	11	Questionable
17	Idiopathic leukopenia	3600	4,400	50	Orally	500	10	Poor
18	Idiopathic leukopenia	1400	1,500	5-15	Orally	125	14	Poor
19	Idiopathic leukopenia	3400	2,700	5-15	Subcutaneous & Orally	270	42	Questionable
20	Idiopathic leukopenia	4100	2,100	50	Orally	500	10	Poor
21	Idiopathic leukopenia	1800	2,500	10	Orally	80	8	Poor
22	Idiopathic leukopenia	2800	2,800	10	Orally	100	10	Poor
23	Idiopathic leukopenia	2500	2,050	20	Intramuscularly	280	14	Poor
24	Irradiation leukopenia, lymphatic leukemia	2600	14,950	3-15	Orally	175	15	See Chart 6
25	Acute leukemia	2500	2,700	20	Subcutaneous & Orally	460	23	Poor
26	Irradiation leukopenia, lymphosarcoma	2700	2,000	20	Orally	200	10	Poor
27	Irradiation leukopenia, Hodgkin's disease	1800	2,800	50	Orally	700	14	Poor
28	Irradiation leukopenia, malignant lymphoma	2200	1,800	50	Orally	500	10	Poor
29	Irradiation leukopenia, cancer of breast	3500	2,300	10	Orally	60	6	Poor
30	Irradiation leukopenia, cancer of thyroid	4800	4,800	15	Orally	150	10	Poor
31	Irradiation leukopenia, cancer of breast	4300	3,300	15	Orally	150	10	Poor
32	Irradiation leukopenia, lymphosarcoma	3400	4,100	50	Orally	500	10	Poor
33	Irradiation leukopenia, cancer of cervix	3300	2,800	15	Orally	150	10	Poor
34	Irradiation leukopenia, lymphosarcoma	3400	2,400	50	Orally	500	10	Poor

Within 6 to 8 weeks the red blood cell count had increased on the average to 292% and the hemoglobin to 269% of the values prior to giving folic acid. No direct counts were made on the number of blood platelets, although from observations made from examination of blood smears, these elements were also noted to increase in number. At the end of 2 to 4 weeks of folic acid therapy, 4 of the 5 cases of pernicious anemia were given parenteral liver extract. No subsequent reticulocyte response was noted in any of these cases.

preparation, it became necessary to give the patient whole blood transfusions and parenteral medication (see Chart 2).

3. Case 6 is the only patient with sprue which we have had the opportunity to treat. As can be seen in Chart 3, the red blood cell count rose from 3.5 million per c.mm. to 5.01 million per c.mm., and the hemoglobin rose from 13.1 gm. % to 14.7 gm. % in 7½ weeks. No reticulocyte response was noted. On the other hand, the clinical improvement was striking for the patient gained strength and weight and his diarrhea subsided.

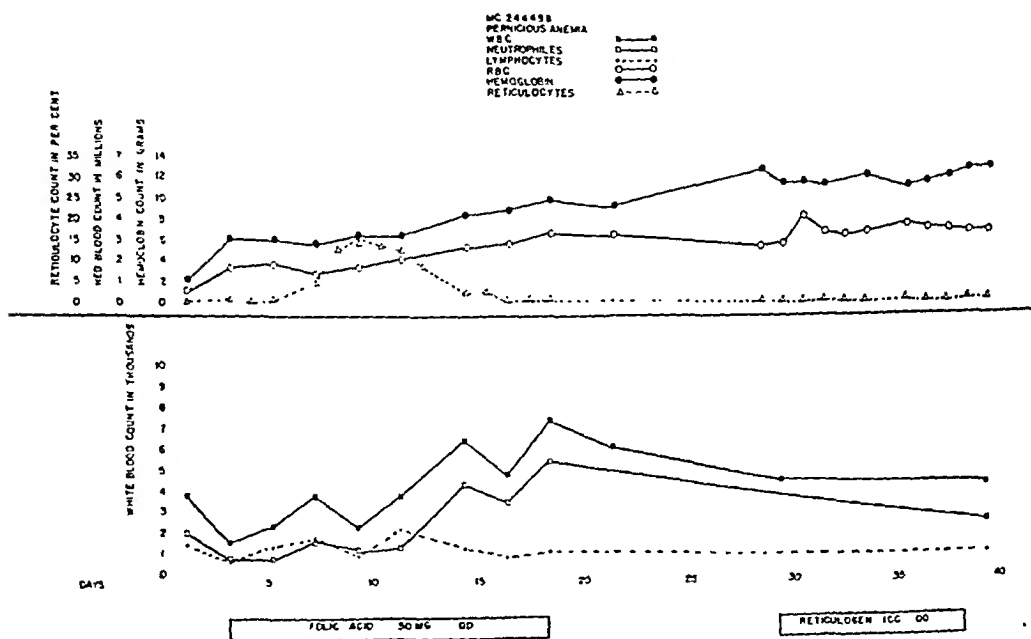


CHART 1.—Response to folic acid in a case of pernicious anemia.

2. The effect of combined preparation of folic acid and iron on a patient with pernicious anemia is represented in Case 1. This preparation was later found to be low in folic acid activity. On the 3rd day of treatment with this combined preparation, the patient developed diarrhea and absorbed little, if any, folic acid, for there was no reticulocyte response and the bone marrow remained megaloblastic in type. The clinical condition became rapidly worse and finally on the 5th day following institution of the combined folic acid-iron

4. In 3 cases of macrocytic anemia of undetermined origin no effect was produced by administration of folic acid (see Cases 7, 8 and 9, Table 2).

5. No beneficial effects were noted on the anemia of 4 cases of renal insufficiency treated with folic acid (see Cases 10, 11, 12, 13, Table 2, Chart 4).

6. The administration of folic acid produced no effect on the leukopenia associated with Addison's disease (1 case) (see Case 14, Table 3).

7. In 1 case of Felty's syndrome no

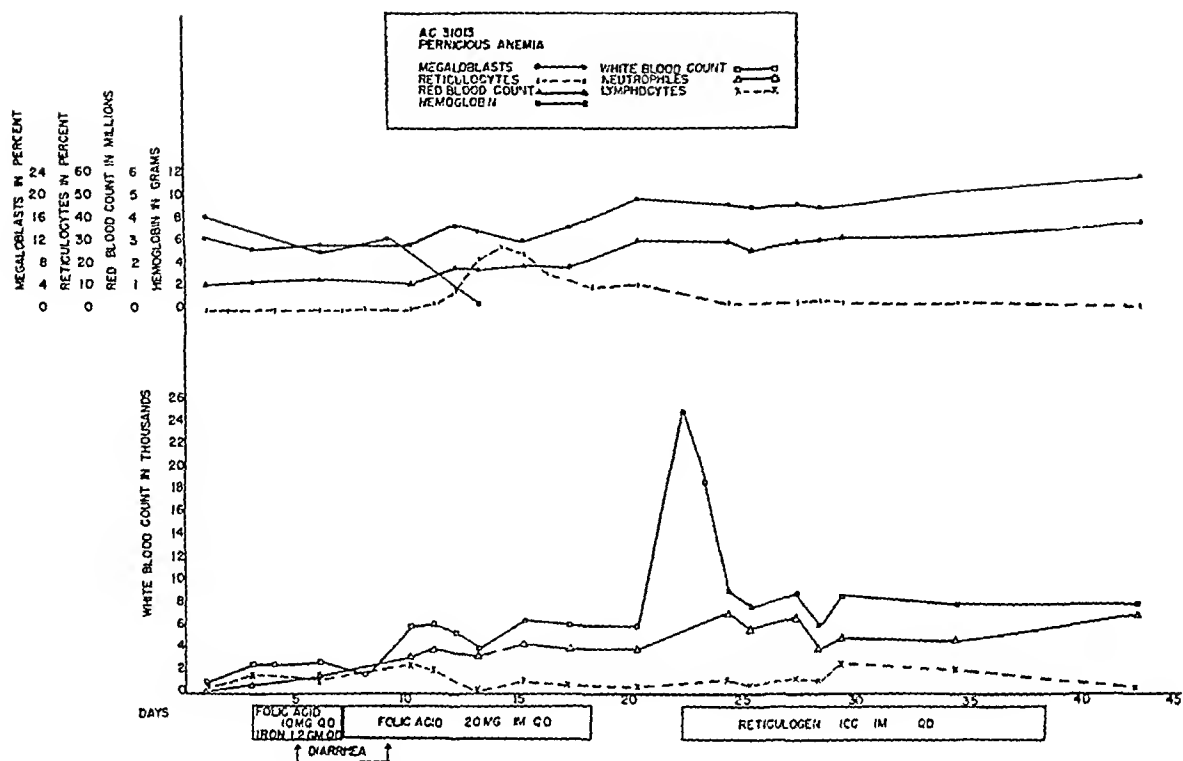


CHART 2.—Delayed response to combined folic acid iron preparation, perhaps due to the interference of iron with the absorption of folic acid.

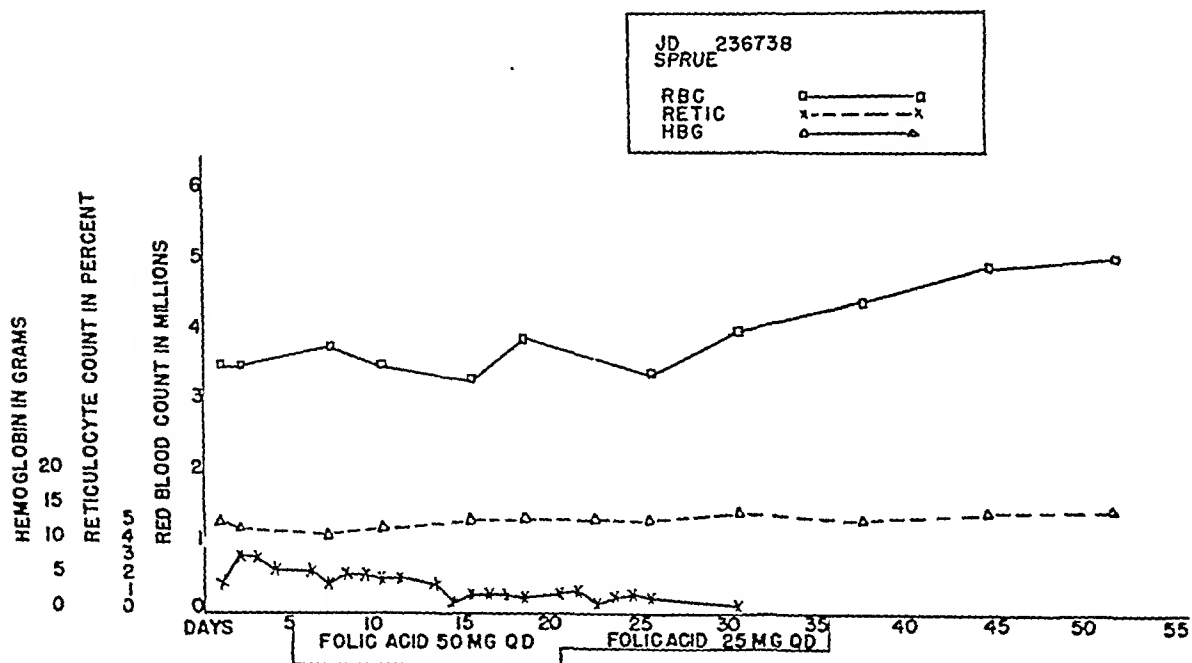


CHART 3.—Response to folic acid in a case of sprue.

effect of folic acid was detected on either the white or red blood cell count (see Case 15, Table 3).

8. In 1 case of agranulocytosis resulting from thiouracil administration for hyperthyroidism, an increase of the white blood cell count was observed 7 days following the oral administration of 50 mg. of folic acid. It should be emphasized, however, that thiouracil had been discontinued at the same time that folic acid was begun (see Case 16, Table 3).

9. Seven cases of idiopathic leukopenia have been studied. These cases were not suffering from the lack of any known nutritional factors, had not been exposed to any material known to be toxic to the

following the administration of oral folic acid. Despite these responses this patient ultimately died and the leukocytosis, although apparently associated with folic acid administration was not permanent. The final counts lapsed to their former levels despite continuation of treatment.

10. Two cases of leukemia have been given folic acid. Case 24, a patient with chronic lymphatic leukemia, was given folic acid because of leukopenia induced by Roentgen radiation. At the start of folic acid treatment his count was 2600. Four days after receiving folic acid (total amount 20 mg.) his white blood cell count had risen to 8000 per c.mm. A second course of folic acid given 1 month later

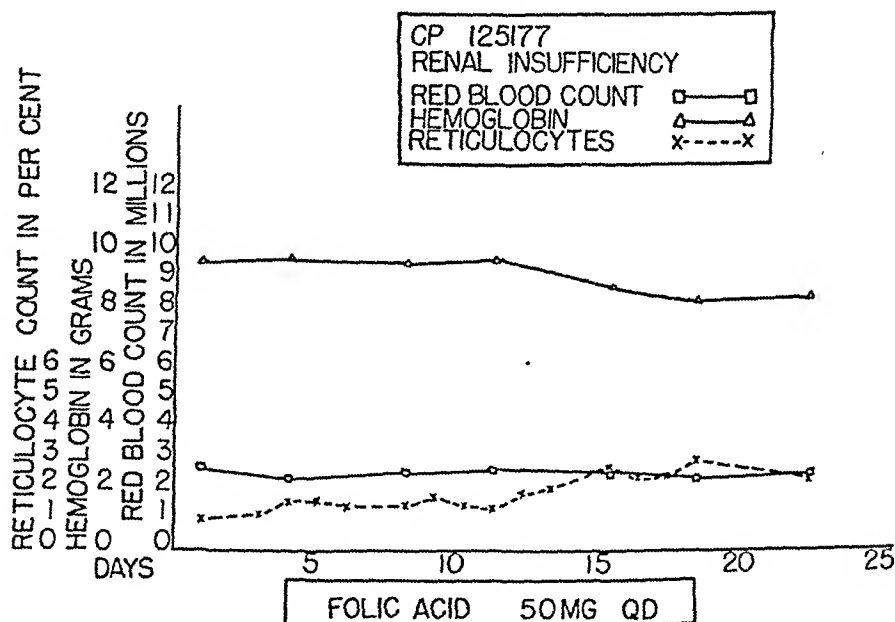


CHART 4.—Failure to respond to folic acid in a case of anemia of renal insufficiency.

bone marrow and on physical examination did not have palpable spleens. Despite numerous diagnostic tests, no satisfactory diagnosis could be established. As can be seen from Table 3 no apparent beneficial effect can be attributed to the administration of folic acid in these cases with the possible exception of Case 19, Chart 5. This child showed a slight, but detectable leukocytic response on at least 2 occasions

had a slight effect on the white blood cell count (see Case 24, Table 3, Chart 6).

Case 25 was a patient with acute myeloblastic leukemia who received 20 mg. of folic acid daily over a period of 23 days. Although there was a transient rise in the hemoglobin and red blood cell count following administration of this drug, the patient succumbed 4 months after the onset of the disease.

11. Nine cases of leukopenia resulting from Roentgen radiation because of various types of malignant disease have been studied. In none of these cases was any effect noted on the level of the white blood cell count following folic acid administration. Chart 7 is representative of this negative effect (see also Cases 26 to 34, Table 3).

Discussion. 1. In our series of cases the best results of folic acid therapy were obtained in cases of pernicious anemia in relapse (see Chart 1). In general, the hematologic response paralleled, but was not identical with, the response obtained in liver-treated cases. These differences have been pointed out by others, Amill and Wright,³ and Frommeyer and Spies,⁹ and Meyer¹⁵ who have shown that the reticulocyte response following folic acid

administration differs from what might be expected following the administration of active liver principle. Chart 8 shows this difference very clearly. In 5 cases of pernicious anemia treated with folic acid, the mean reticulocyte curve was not as high as was obtained in a comparable group of cases of pernicious anemia treated with potent liver extract. The chart also shows that in the folic acid treated group the reticulocytes tended to remain elevated over a longer period of time.

Recently Frommeyer and Spies⁹ and Heinle and Welch¹⁰ have observed that folic acid may not control the neurologic manifestations of pernicious anemia. In fact neurologic relapses have developed during folic acid administration. Although we have had no experience with the prolonged treatment of pernicious anemia

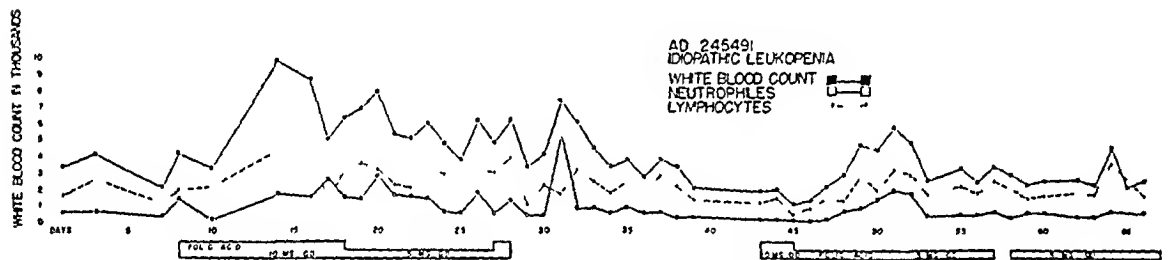


CHART 5—Questionable temporary effect on the white blood count in a case of idiopathic leukopenia in an infant.

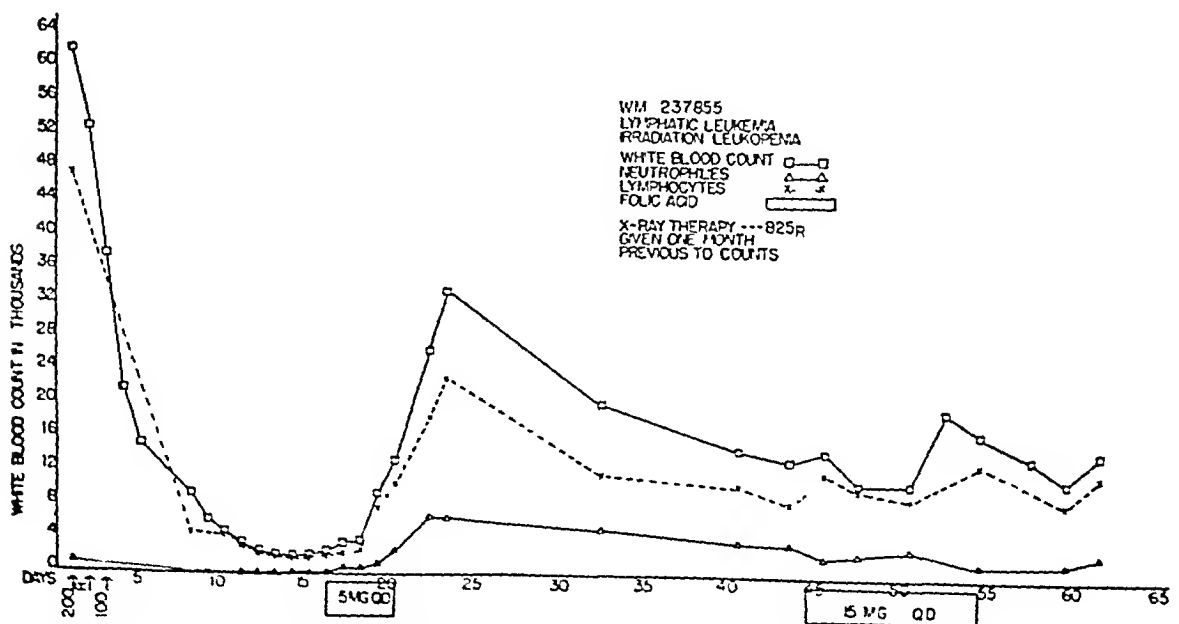


CHART 6.—The effect of folic acid upon a case of chronic lymphatic leukemia in which leukopenia resulted from Roentgen treatment.

with folic acid it has been observed by us that the paresthesias so characteristic of this disease show little tendency to clear following administration of this drug (see Case 5). The answer to this interesting problem will have to await further study.

2. In this group of cases of pernicious anemia, Case 1 was of particular interest to us. This patient received a combined

folic acid-iron preparation which was later proved to be low in folic acid activity. The iron caused diarrhea and thereby might have impaired the absorption of folic acid given by mouth. This fact was supported by the observations that no reticulocyte increase was detected and that the bone marrow remained megaloblastic in type.

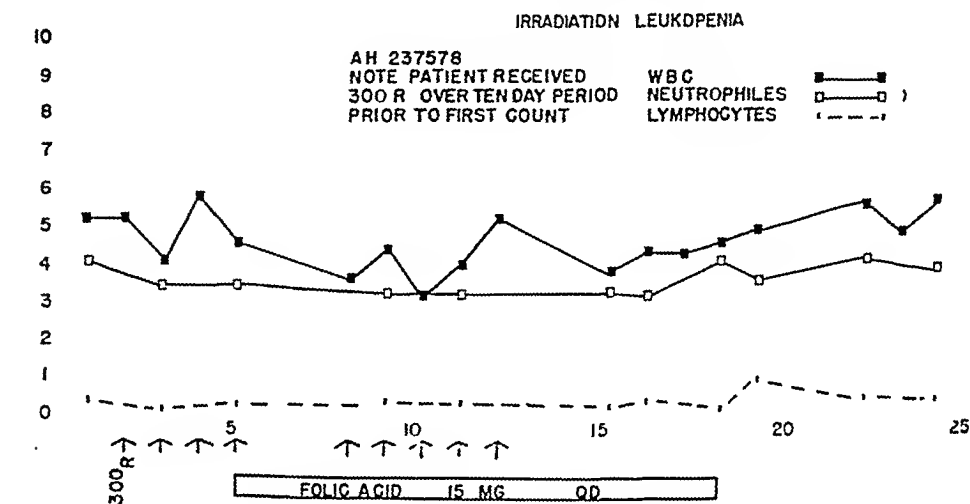


CHART 7.—Failure to respond to folic acid in a case of metastatic carcinoma of the thyroid given Roentgen treatment.

A COMPARISON OF THE MEAN RETICULOCYTE RESPONSE

IN FIVE PATIENTS TREATED WITH INTRAMUSCULAR

LIVER EXTRACT AND ORAL OR INTRAMUSCULAR FOLIC ACID

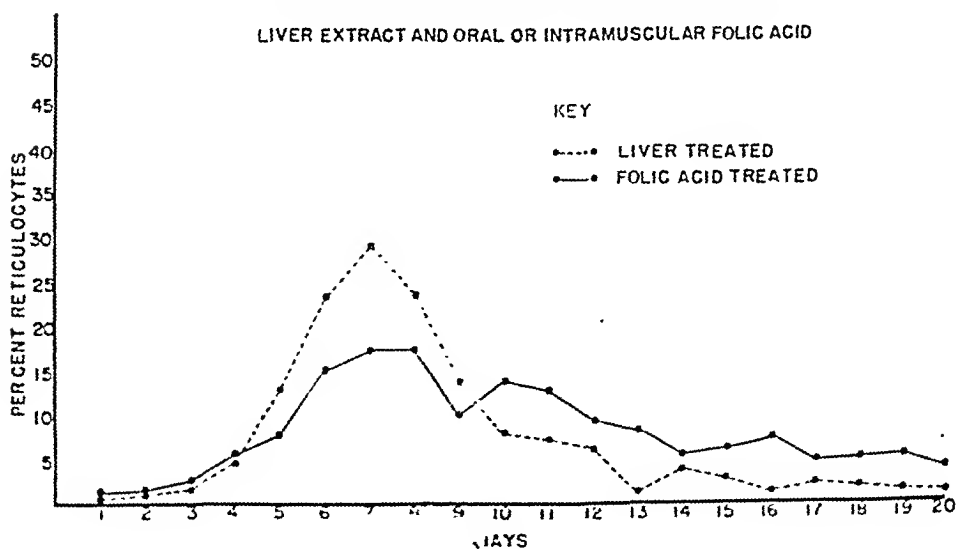


CHART 8.—Self-explanatory.

It is true that in some cases of pernicious anemia the iron stores may be depleted, but since this is not the fundamental defect in this disease it seems unwise to jeopardize the absorption of folic acid by the use of a combination of this drug with iron (see Chart 2).

3. The favorable effect of folic acid upon sprue has been reported by Darby and Jones,⁴ and Spies, Menendez *et al.*¹⁹ who have shown marked hematologic and clinical improvement in patients who were treated for this disorder. For experimental purposes their patients were placed on diets low in protein and poor in vitamin B substances and were then given folic acid. Prompt clinical and hematologic improvement occurred. Their patients gained strength and weight, exhibited a pronounced reticulocyte response and experienced a cessation of their distressing bowel complaints. Except for failure to produce a reticulocyte response, our single case showed a similar tendency to improve following folic acid administration. It can be seen in Chart 3 that the patient's red blood cell count rose slowly. Perhaps the reason why a more striking hematologic improvement was not noted was because the patient was not profoundly anemic upon admission. However, the clinical improvement was quite satisfactory.

4. The mere existence of a macrocytic anemia does not imply that there will be a beneficial response to folic acid. For example, the 3 cases of macrocytic anemia of undetermined origin (Cases 7, 8 and 9) showed no response to folic acid administration. No elevation of the reticulocyte count or the red blood cell count was noted in these cases. In our experience, as in the experience of others,^{21,22} the seeming prerequisite for a beneficial response to folic acid on the part of the red blood cell picture is a megaloblastic arrest as seen in the bone marrow. This may not be true in all cases but for the present at least this observation seems to be correct.

5. Numerous theories have been propounded as to the mechanisms of the

production of anemia in chronic nephritis. Hematuria, bleeding into the tissues, hemolysis, loss of albumin, dietary deficiency in protein, direct toxic action on the bone marrow, insufficient blood regeneration, have all been implicated. Those who have studied the bone marrow in this type of anemia seem to agree that ultimately there is a selective erythroid hypoplasia which in some manner is associated with the azotemia. It is generally accepted that the severity of the erythroid hypoplasia and anemia is correlated with the degree and duration of the azotemia. In our cases early in the course of chronic nephritis the bone marrow may be normoblastic in type but subsequently there is an exhaustion of the erythroid elements and a tendency towards hypoplasia. It is interesting to note in our series of cases there was a slight but persistent reticulocytosis prior to the administration of folic acid. In none of the 4 cases in which this drug was used was there any hematologic response. We have no good explanation for the anemia of renal insufficiency or for the reticulocytosis which we have observed in this condition. We believe that a more extensive search should be made for a hemolytic factor which may play some rôle in this type of anemia.

6. It has been stated by Albright *et al.*⁷ that patients with Addison's disease exhibit a relative neutropenia and lymphocytosis in comparison with normal figures. Accordingly, it was thought to be of interest to study the effect of folic acid in this condition. No effect was noted on either the total white blood cell count or the differential formula in the 1 case which has been treated. Although the fundamental hemopoietic defect which may cause leukopenia in Addison's disease is unknown, we would expect that folic acid would not correct the neutropenia which sometimes occurs in this condition.

7. Little is known concerning the mechanism of leukopenia in Felty's syndrome. It is known that splenectomy does not produce lasting benefit in these

cases so that so-called "hypersplenism" is probably not an important factor. In the 1 case which was treated, folic acid had no effect on either the anemia or the leukopenia.

8. One case of agranulocytosis resulting from administration of thiouracil was studied. The apparent effect of folic acid in bringing about an elevation of the total white blood cell count in this case, we do not wish to attribute to folic acid. It was probably the result of removal of the patient from thiouracil treatment. The evidence is good at the present time that folic acid is neither of benefit as a prophylactic or therapeutic agent for the agranulocytosis produced by thiouracil.

9. Seven cases of "idiopathic" leukopenia have been treated. In 6 cases the results of treatment were entirely negative. There was no alteration of the total white blood cell count or the differential formula. In Case 19 (see Chart 5) there seemed to be a response to folic acid as the total white blood cell count and the number of granulocytes increased in number on 2 separate occasions. However, this effect was transitory and the patient ultimately succumbed despite continuation of folic acid medication. The poor results obtained in this group are consistent with the findings of Doan,⁸ and Spies²⁰ who have noted little or no effect of folic acid in cases of "idiopathic" leukopenia treated with folic acid.

10. We have treated 2 cases of leukemia with folic acid. As noted under Results, Case 24 was a patient with chronic lymphatic leukemia who was given folic acid because of a leukopenia induced by Roentgen radiation. The white blood cell count returned promptly to high levels (see Chart 6). It cannot be said whether this represented a true response to folic acid or whether it was mere coincidence.

The second case of leukemia which has been studied—a case of acute myeloblastic leukemia (Case 25)—was given folic acid in a leukopenic phase of the disease. Despite an apparent remission characterized

by a feeling of well-being and an increase in the red blood cell count and hemoglobin values, this patient succumbed 4 months after the recognition of his disease. This poor result is typical of the findings of others^{20,26} who have obtained similar observations in the folic acid treatment of leukemia. However, as suggested by Case 24, there may be some rationale in giving folic acid to those cases of leukemia which develop leukopenia in the course of Roentgen ray therapy. This, of course, cannot be established from the findings in 1 case.

11. Many investigators^{12,14,24,25} have shown the importance of folic acid in maintaining the normal white blood cell count. Considerable importance has also been attached to the study of the living organisms' ability to respond to folic acid when exposed to certain conditions of stress. One of the most important of these studies has been the surprising observations of Watson, Sebrell, McKelvey and Daft²² who noted the correction of leukopenia induced by Roentgen radiation following the administration of folic acid. They reported favorable results in 7 out of 8 cases so treated, but state their results were not conclusive and that further investigation was indicated. Nine cases of leukopenia of this type have been treated. In none of these cases have we obtained a correction of the leukopenia by the use of folic acid. It is difficult to understand how folic acid would be of use in correcting this type of leukopenia, but it must be admitted that in a certain few cases there may be a nutritional factor which is in part responsible for the low white blood cell counts. In these certain few cases folic acid may be of some benefit.

Summary. Results of a study of 34 cases of varying types of blood dyscrasias treated with folic acid show that: 1. Folic acid will correct the abnormal blood findings in cases of pernicious anemia in relapse.

2. It is likely that the neurologic manifestations of pernicious anemia are not

corrected by folic acid.

3. In pernicious anemia the reticulocyte response in liver treated patients differs from that obtained in folic acid treated patients.

4. It is probably unwise to combine folic acid and iron in the treatment of pernicious anemia.

5. Sprue responded favorably to folic acid administration (1 case).

6. All macrocytic anemias do not respond to the administration of folic acid. In those cases in which there is a megaloblastic arrest in the bone marrow, favorable results can be anticipated.

7. Folic acid did not affect the anemia associated with chronic nephritis.

8. The administration of folic acid did not alter the leukopenia associated with either Addison's disease or Felty's syndrome (1 case each).

9. The apparent effect of folic acid upon the level of granulocytes is 1 case of thiouracil agranulocytosis was probably coincidence for others have reported no effect.

10. Folic acid had no effect on the leukopenia of idiopathic states.

11. No beneficial effect was noted in 2 cases of leukemia treated with folic acid.

12. Folic acid did not correct the leukopenia induced by Roentgen radiation.

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PHARMACODYNAMIC PROPERTIES OF PENICILLIN PREPARATIONS WITH PROLONGED ACTION

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WE suggested recently⁶ a penicillin mixture for clinical use which has the advantage of prolonged action, high fluidity, and readiness for injection with an ordinary syringe. The standard preparation recommended for human use consists of a suspension of 300,000 u. crystalline potassium penicillin in 1 cc. vegetable oil containing 0.3 mg. epinephrine. This is a milky suspension, available in vials and ampules, which can be injected with a 20 to 21 gauge needle.

A clinical evaluation of the efficiency of this suspension in cases of male gonorrhea, conducted by Cohn and Kornblith,³ confirmed the advantages claimed. Investigations on the activity of this penicillin composition in other infections are in progress: one may anticipate that the clinical results will be parallel to those of Cohn and Kornblith, *i. e.*, increased activity, determined by the repository effect.

The present paper contains a number of observations gained in the course of our study; some of these have a general interest concerning the relationships (a) between dosage and penicillin levels, rate of absorption, dosage and animal species, size of the individual, etc.; (b) between blood and tissue levels; and (c) between systemic and local effects of the vasoconstrictor.

Material and Methods. In dog, rabbit and man, 1 or 2 cc. of the material was injected intramuscularly (if not otherwise

stated) into the buttocks. In the rat 0.1 cc. was consistently injected intramuscularly. Blood samples were withdrawn at various intervals after treatment and their penicillin content determined by the serial dilution method,¹¹ using rabbit blood as indicator for the growth of *Strep. hemolyticus*, Type A, Group 3. The minimal penicillin concentration which inhibited the growth of this microorganism varied between 0.015 and 0.03 u. per cc., which is the usual sensitivity of the method. The blood was withdrawn from the jugular vein of dogs and rabbits, from the subaxillary artery of the anesthetized rat, and from the eubital vein of man. The organs of rats were removed after the animal was thoroughly bled; their penicillin content was determined with the dilution method on the tissue Bray, ground with sand in a mortar and diluted with twice its weight in 1% phosphate buffer pH 6.

Results. The following observations are based on approximately 200 experiments on dogs, 120 on man, 50 on rabbits and 400 on rats.

1. INFLUENCE OF THE VEHICLE ON THE BLOOD LEVEL. We determined, in the first place, the influence of the vehicle in which the penicillin is injected on the blood levels. Representative data for the following media are summarized in Figure 1: (a) saline, (b) peanut oil, (c) water/oil emulsion similar to that recommended by Freund and Thomson:⁴ (peanut oil + 25% of a cholesterol ester preparation (Falba or Amerchol) emulsified by the addition of 25 to 50% saline), (d) peanut oil + 4.8% beeswax, and (e) ethyl oleate + 4% beeswax.

It appears that with the penicillin dosages used in clinical practice (200,000 to 300,000 units) oil alone and the water/oil emulsion give no prolongation of the blood level compared to the administration of aqueous solutions of equal dosage. This observation is in agreement with the report of Harris, Wilcox and Finland.⁹ Similarly, aqueous gelatin, up to 50%, does not induce any prolongation of the penicillin level. The peanut oil beeswax mixture, recommended by Romansky¹² exerts, as known, a great retaining power which is entirely due to its beeswax content.

Two cc. of 4% beeswax in ethyloleate containing 250,000 u. Ca-penicillin (English preparation) gave shorter durations than 300,000 u. in 1 cc. of 4.8% in peanut oil. The shorter duration of the English preparation probably depends on the relative concentration of penicillin per cc. as the experiments of Ungar¹⁴ suggest rather than on the dosage difference.

2. INFLUENCE OF THE VASOCONSTRICTOR DOSAGE ON THE BLOOD LEVEL. After having established the influence which the character of the vehicle exerts on the absorption speed of intramuscularly injected penicillin, the effect of vasoconstrictors incorporated into the various media was studied.

In the early part of the investigation, we noticed that extremely small doses of epinephrine incorporated in the emulsion, or in the oil, induced a very definite prolongation of the blood level. Since a mixture of penicillin and epinephrine can be prepared as a stable oily suspension, we determined on experimental animals the quantitative relation between the duration of penicillin blood level and the epinephrine content. (Fig. 2.) A prolonging action of 0.01 mg. epinephrine on the duration of the blood level was already noticeable; this action increases with increasing epinephrine dosage, up to a "ceiling" dosage (0.2 to 0.3 mg.), where a further increase of epinephrine is without effect on the duration. The ceiling in the prolonging effect of the vasoconstrictor might depend on a *maximal* ischemic reaction of the surrounding tissue.

In man we compared the effect of 0.25 mg. and 1 mg. epinephrine given subcutaneously with 300,000 units penicillin in 1 cc. oil.

The differences found in duration were in the range of the individual variations. Thus it seems that this ceiling dose for the local effect of epinephrine is the same in man as in dog.

3. INFLUENCE OF THE PENICILLIN DOSAGE (IN OIL WITH VASOCONSTRICTOR). The blood level curves seem to indicate that following penicillin administration in oil containing vasoconstrictor the duration of the blood level increases proportionately up to only a certain penicillin dosage. This ceiling dosage is approximately 200,000 u. for the dog and 300,000 u. for man, which in the 2 species gives a 1 day level.

In man, by increasing the intramuscular dose from 200,000 to 300,000 u., the length of the blood level is increased by 5 to 9 hours, while the increase of duration is only from 1½ to 3 hours when the 300,000 u. dose is brought to 600,000 u. This increased dosage induces, however, without substantially influencing the duration, blood penicillin curves running at higher levels.

The blood levels following the administration of penicillin in oil with vasoconstrictor are quite high for a prolonged period (10 to 15 hours), after which the progressive descent of the blood curve starts. Figure 3 shows the great increase of the blood levels in man during the first 15 hours following the administration of penicillin in oil + vasoconstrictor as compared to saline.

Similar are the observations on dogs. By increasing the 200,000 u. dosage to 300,000 u. the average duration increases from 18½ to 22 hours; by increasing it to 400,000 u. the duration reaches up to 24 hours.

In dog, as in man, by the use of an oily vehicle with vasoconstrictor high initial blood levels were maintained for long periods, generally for over 10 hours. The following examples illustrate the extent of this high initial "plateau."

Dog No. 2039—weight 9.6 kg.

Injected with 200,000 u. potassium penicillin in 1 cc. oil and 0.05 mg. epinephrine:

Hours after injection	Serum levels (units/cc.)
2½	4 0
4½	12 0
6½	4 0
16	0 5

Dog No. 2056—weight 8 kg.

Injected with 300,000 u. potassium penicillin in 1 cc. oil and 0.2 mg. epinephrine:

Hours after injection	Serum levels (units/cc.)
1	9.0
3	20.0
7	8.0
17	1.0

The same dog, No. 2056, injected with a higher dose, *i. e.*, 400,000 u. crystalline potassium penicillin in saline, has, in contrast, the following concentration:

Hours after injection	Serum levels (units/cc.)
1	9.0
3	9.0
7	0.03
8½	0.0

Two other important facts are visible from these examples, namely, that in the dog at least, following the injection of penicillin in oil with vasoconstrictor, the blood concentration reaches the same height as that obtained with penicillin injected in saline, though the appearance of the peak is delayed. In the examples presented, the peak effect is reached 3 to 4½ hours after injection of the oily suspension with vasoconstrictor. This value represents the average recorded in our various experiments: minimum 2 hours; maximum 7 hours.

In our animal experiments we do not find any impressive differences between various penicillin salts (crystalline potassium and sodium penicillin; amorphous calcium penicillin) when suspended in oil epinephrine medium in regard to the duration of the blood level. However, a somewhat shorter duration following intramuscular injection of calcium penicillin into man is found by Dr. Queally in comparison to that seen with the crystalline potassium salt. (The durations with Calcium penicillin in man are similar to those obtained with commercial preparations of Ca-penicillin in peanut oil containing 4.8% beeswax.) This finding is in agreement with various reports concerning the shorter blood level following administration of the amorphous calcium salt of

penicillin compared to the crystalline material administered in this mixture.⁵ The particle size of the crystalline material has no influence on the duration in dogs injected intramuscularly with 300,000 u. This is at variance with the results reported for the liquid POB mixture, and similar to the findings with the solid mixture.⁵

4. BLOOD LEVEL IN DIFFERENT SPECIES. The duration of the demonstrable blood penicillin level is approximately the same in man and dog, if equal doses (300,000 to 600,000 u.) of potassium penicillin in oil epinephrine are given. Accordingly, the minimal dose required to obtain a 1 day duration calculated on the basis of body weight is inversely proportional to the size of the species. For the rat this dose is 100,000 u. per kg.; for the rabbit about 30,000 u. per kg.; for the dog 25,000 u. per kg.; for man 4000 to 5000 u. per kg.

Generally speaking, it is not the *relative* but the *absolute* dose injected which determines the prolongation of the penicillin effect. This is particularly apparent in observing the duration following the injection into dogs of doses used in human therapy.

The same total amount of penicillin absorbed during an approximately equal time period—considering a fairly similar rate of elimination—results in higher blood concentrations in the species of smaller size. This statement is based on the figures of Table 1.

The individual variations are as wide in experimental animals as in man. For instance, in dogs treated with 300,000 u. (in 1 cc. oil + 0.2 to 0.4 mg. epinephrine) the shortest blood level is 16 hours duration, the longest 26 hours. In man, treated subcutaneously with 600,000 u., the shortest duration is 18 hours, the highest so far recorded over 25 hours.

5. DURATION OF PENICILLIN IN TISSUES. The urines of the subjects treated with penicillin in oil with vasoconstrictor contain relatively high amounts of penicillin after the drug ceases to be detectable in the blood. The following example is characteristic: 3 male subjects treated Tuesday 10 A.M., with 300,000 u. in 1 cc. oil containing 0.3 mg.

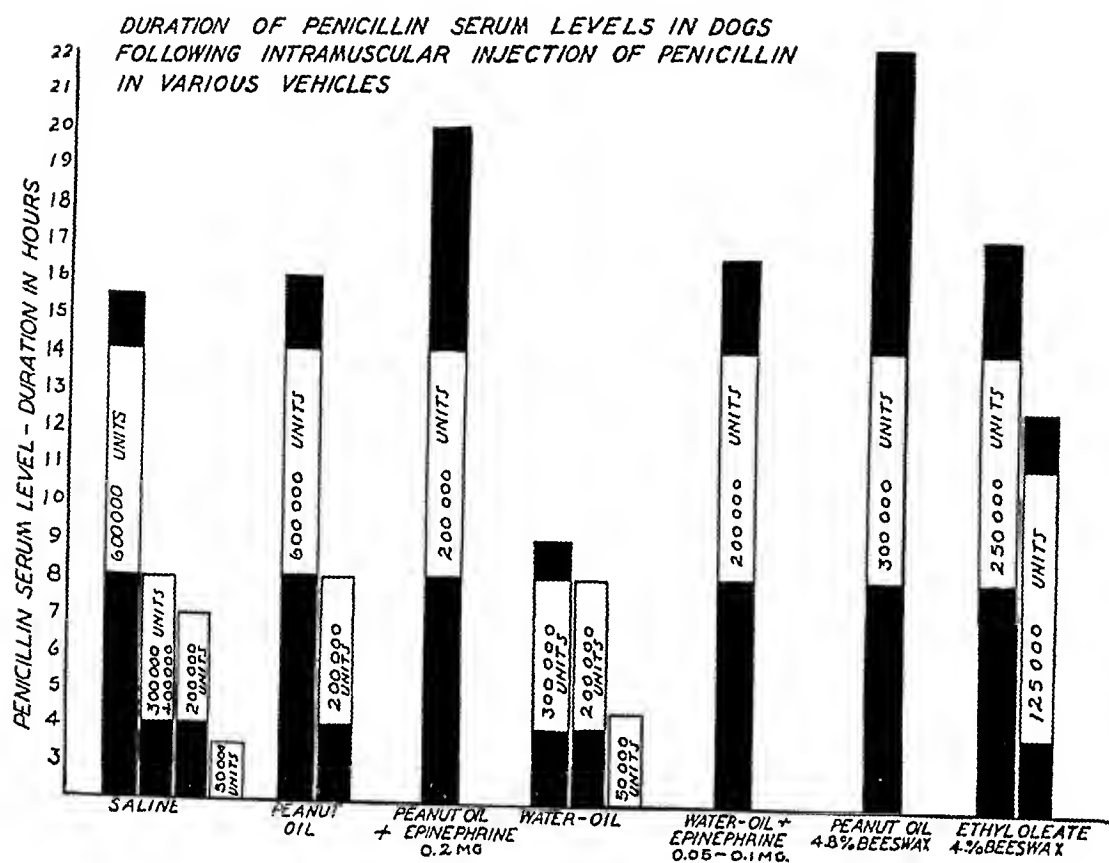


FIG. 1

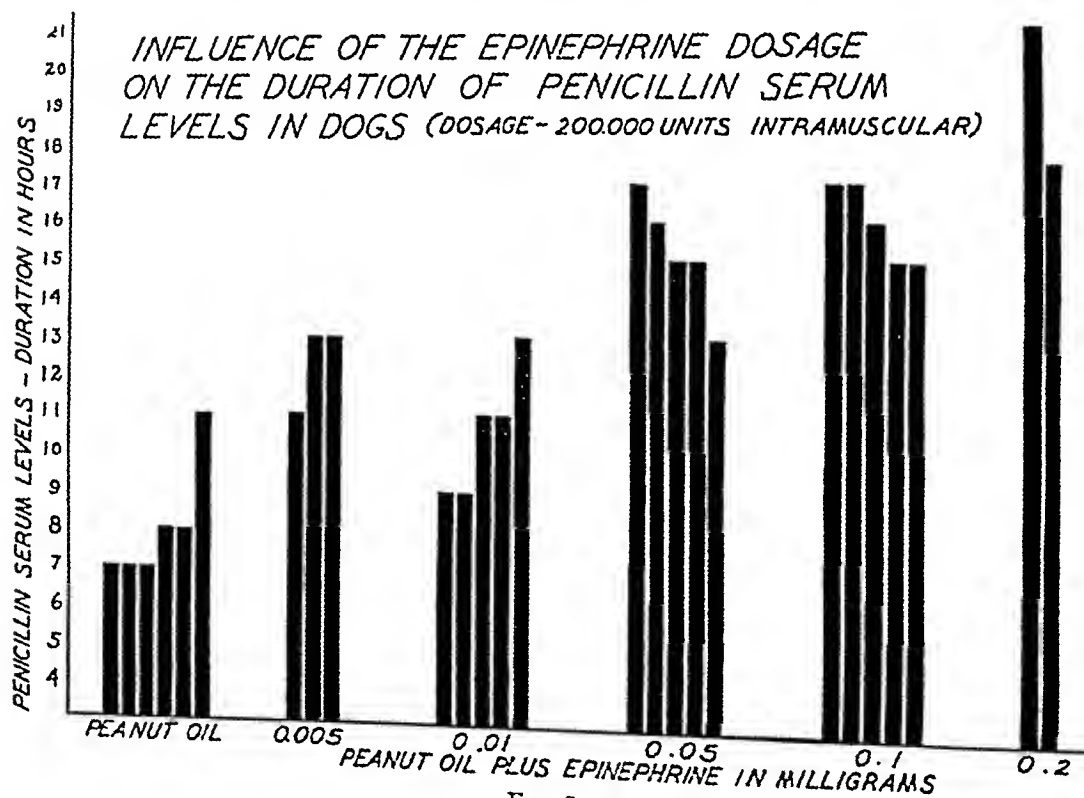


FIG. 2

epinephrine; 7 hours after injection: blood level 0.63, urine 375 to 600 u.; Wednesday noon: blood samples negative; urine samples: 0.5 to 1.8 u. per cc.; Thursday noon: 0.1 u. per cc. in urine. This delayed elimination of penicillin in the urine seems to be a general characteristic of repository penicillin administration, since similar observations were reported for the peanut oil beeswax mixture by Romansky.^{12,13}

The presence of penicillin in the urine after the blood became negative led us to investigate its duration in the tissues. Experiments on rats reveal that the duration of the penicillin level is much more prolonged in the liver and kidney than in the blood. (See Fig. 4.)

oil containing 0.06 mg. epinephrine given 3 hours before injection protected the majority of mice. This is a high degree of prophylactic effect compared to that of an aqueous solution, which gives no protection at all in doses of 2000 u. per 20 gm.

A certain improvement in the protective effect was noticed also using peanut oil suspensions of penicillin. To obtain this effect, however, the doses of penicillin required are 2 times higher than in the presence of a vasoconstrictor.

(b) *Experimental Rabbit Syphilis.* Rabbits with acute testicular lesions, infected as described by Ercoli and Lafferty,⁷ were treated intramuscularly with various doses of penicillin in oil with epinephrine.

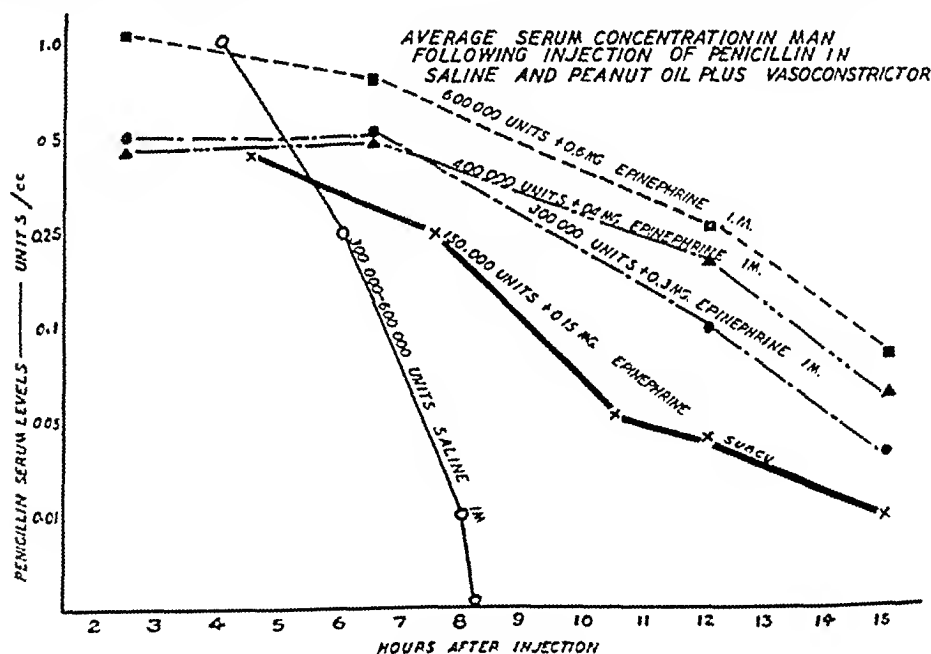


Fig. 3

6. CHEMOTHERAPEUTIC ACTIVITY IN EXPERIMENTAL INFECTIONS. (a) *Pneumococcus Type II.* The duration of the prophylactic effect of various doses of penicillin in oil + vasoconstrictor was compared with that following administration in saline or in oil alone.

Mice were infected intraperitoneally with 1000 lethal doses of *pneumococcus 6392*, as described by Buck and Schmitzer,¹⁴ at various intervals after spontaneous treatment. Doses of 5000 u. per 20 gm. injected in 0.5 cc.

The smallest dose used, 1 single injection with 10,000 to 25,000 u. per kg., induced rapid disappearance (6 to 12 hours) of the spirochetes and regression of the syphilitic lesion (4 to 8 days) in all 6 rabbits treated. For the quantitative evaluation of curative activity we must await the results of the lymph node transfer.

7. PHARMACOLOGIC EVALUATION OF VASOPRESSOR ACTION. As known,¹⁵ the oily vehicle interferes with the intensity of the systemic action of epinephrine. We re-

ported⁶ the absence of vasopressor activity in man of penicillin preparations containing 0.6 to 0.8 mg. epinephrine, *i. e.*, twice the dose contained in the standard preparation. A large number of tests on anesthetized cats, carried out by Dr. R. J. Schachter, with the usual pharmacologic methods, showed that the intramuscular injection of 2 mg. epinephrine in 1 cc. oil, corresponding to 0.6 to 0.7 mg. per kg. cat, does not produce a detectable increase of blood pressure. Only by massaging the site of the intramuscular injection is an increase of 7 to 32 mm. in the carotid blood pressure obtained when doses of 0.5 to 1 mg., or higher, are used.

Discussion. Injected in oily suspension, the effect of epinephrine on the blood pressure is noticeably diminished, while

nite amount. The "ceiling duration dose" for epinephrine is approximately 0.2 mg., while for penicillin it varies with the species. The existence of a ceiling dose for epinephrine is apparently related to the production of a *maximal* ischemic action on the surrounding tissue. It is more difficult to advance reasons for the "ceiling duration dose" of penicillin. This is probably determined by various factors: an end-point in the epinephrine effect, the dispersion of the oily material, the instability of penicillin. An additional factor might be represented by the rate of absorption of penicillin from the *deposit*. There is some justification for the assumption that the fraction of penicillin absorbed

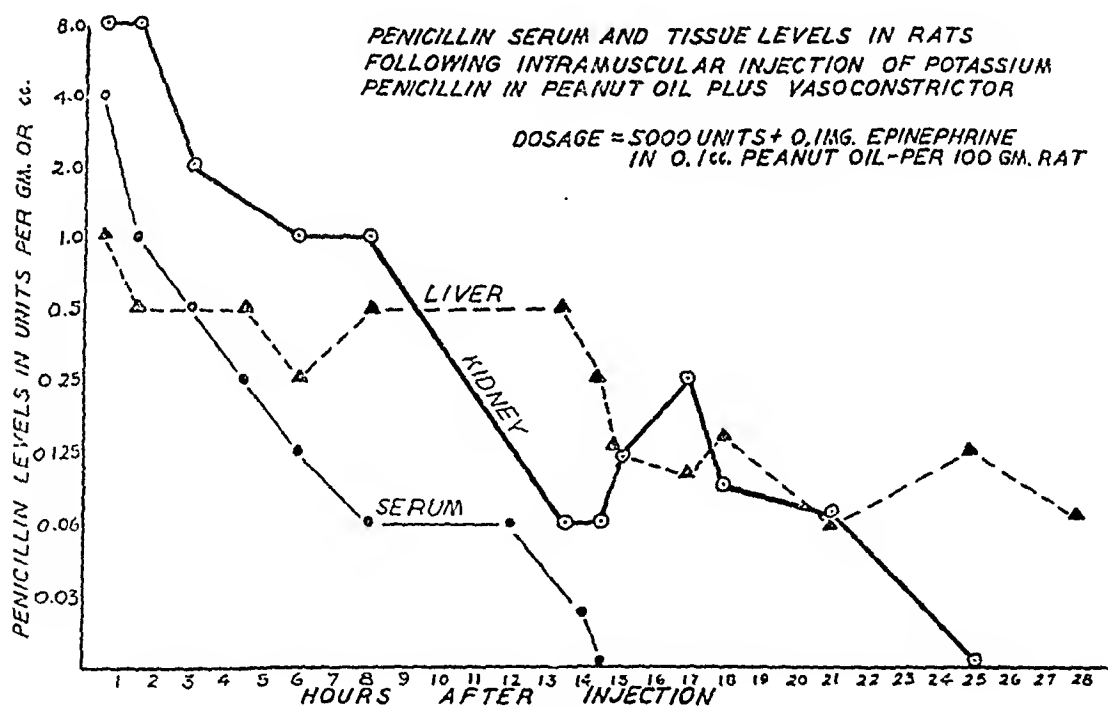


FIG. 4

its delaying action on the absorption of penicillin remains extremely high. The latter effect, which depends on a local ischemic reaction, appears with doses of 0.05 to 0.1 mg., *i. e.*, about one-twentieth or one-fortieth of the dose required for eliciting a systemic vasopressor action.

The duration of the blood level cannot be prolonged beyond a certain ceiling period (26 hours) by increasing the dose of epinephrine and penicillin above a defi-

in equal time intervals does not change with the absolute amount of penicillin in the tissues, when given in oil epinephrine. Supposing that half of the penicillin present in the tissue is absorbed in 2 to 3 hours, the redoubling of the dose would cause an increase of the duration by 2 to 3 hours only.

With the larger *relative* doses required to produce an equal duration in the smaller species, the amounts of penicillin absorbed

during the same time period are correspondingly larger and this obviously brings about higher blood concentrations. In fact, the relation in the peak concentrations reached with a 300,000 u. dose, which gives a 1 day duration in man and in dog, is proportional to their weight differences: 0.5 to 1 u. in man, 5 to 20 u. in dogs. Similarly, an increase of dosage from 300,000 to 600,000 u. in man results in correspondingly higher blood levels. These differences in duration, according to species and relative weight, are important from a methodologic standpoint: one has to consider them when the prolongation obtained with a new preparation is interpreted.

of the initial high concentrations.

The therapeutic value of this "plateau" of high blood levels appears from the following consideration based on the clinical results of Colin and co-workers in the treatment of gonorrhea. The active intramuscular dose which cures practically all (97%) cases of male gonorrhea is 0.5 cc. of our standard preparation corresponding to 150,000 u. of penicillin.³ The "duration" of detectable blood level following such an injection is from 8 to 12 hours. Twice this dose, *i. e.*, 300,000 u. of penicillin injected in saline results, on the other hand, in an unsatisfactory cure rate,⁴ though the duration of the *detectable* blood level is similar, 8 to 9 hours, and

TABLE 1.—PEAK SERUM CONCENTRATIONS IN DOG AND MAN FOLLOWING INTRAMUSCULAR ADMINISTRATION OF PENICILLIN IN SALINE AND IN PEANUT OIL PLUS VASOCONSTRICTOR

Total dosage (units)	Man			Dog		
	Units per kg.	Vehicle	Serum levels (units per cc.)*	Units per kg.	Vehicle	Serum levels (units per cc.)
200,000 . . .	2500	Saline	†	20,000	Saline	5 0-20 0
		Oil + Vasocon.	0.3-1.25		Oil + Vasocon.	1.2- 5 0
300,000 . . .	4200	Saline	>1 25†	30,000	Saline	10 0
		Oil + Vasocon.	0 6		Oil + Vasocon.	1.2-10 0
400,000 . . .	5700	Saline	†	40,000	Saline	10 0-20 0
		Oil + Vasocon.	0 6-1.25		Oil + Vasocon.	2 5-10 0

* The serum levels are the averages of a large number of determinations.

† In man the initial maximum concentrations in saline were not determined. The initial *transitory* peaks correspond to 4 to 5 units per cc.⁹

The experimental work on rats reveals that the prolongation of the penicillin in the organs, liver and kidney, outlasts by long periods the duration of the demonstrable blood level following injections in oil with vasoconstrictor. One might assume that the penicillin present in the organs—after its presence in the blood is no longer *detectable*—is of some therapeutic significance. A certain number of experiments carried out in this laboratory would indicate that the accumulation of penicillin in the organs, such as observed following treatment in oil with vasoconstrictor, cannot be obtained with high doses of penicillin given repeatedly in saline.

The experimental data suggest that the therapeutic advantages of the new penicillin preparation investigated depend on the protracted duration of the antibiotic in the tissues, and on the long "plateau"

the initial (very transitory) peaks are even higher.

Therefore, a comparison of the "duration" of blood levels with these 2 treatments does not provide a satisfactory explanation of the therapeutic differences. The curative effect of the 150,000 u. preparation, in contrast to the 300,000 u. given in saline, is due probably to the plateau effect at relatively high blood levels. This conclusion is in agreement with the data of Buck, Ercoli, Kelly, Lewis and Schnitzer² in experimental pneumonia: "the very high initial peak which was only observed after parenteral administration was of lesser significance than the consistent level of comparatively low concentration to be found in the serum during the hours following the subcutaneous as well as the oral administration."

The more prolonged retention of the

penicillin in the organs, as indicated by the urine levels, is probably an additional factor responsible for the increased therapeutic effectiveness of the suspension in oil with vasoconstrictor.

Summary. 1. The duration of the detectable penicillin blood level is not significantly increased when 200,000 to 300,000 u. are injected in oily suspension or emulsion, as compared to saline. The addition of very small doses of epinephrine to the oily suspension gives a noticeable increase in the blood level duration.

2. The systemic vasopressor activity of epinephrine is diminished by the oil, with the result that small fractions, one-twentieth to one-fortieth, of the therapeutic epinephrine dose prolong the penicillin levels.

3. Compared to the approximately one

day duration of the blood levels, the urines of the subjects treated with 300,000 units of penicillin (in oil + vasoconstrictor) contained penicillin up to $2\frac{1}{2}$ to 3 days. In experimental animals, it was found that the treatment with this penicillin preparation gives about 2 times longer durations in the organs than in the blood.

4. The quantitative aspect of the blood level curves in relation to the dosage was studied. It is assumed that the improved therapeutic activity depends on the prolongation of the penicillin content in the organs and on the initial "plateau" levels in the blood.

5. Prophylactic experiments in mice infected with pneumococcus Type II indicate also an increased duration of therapeutic effectiveness of the penicillin preparation in oil and vasoconstrictor.

The authors wish to express their appreciation to Dr. R. J. Schachter for a number of blood pressure determinations, to Dr. F. Queally of the Medical Division of William R. Warner & Co., for many experiments on human volunteers, to Drs. A. Cohn and B. A. Kornblith for sending blood samples of their cases, to Miss Margaret Whitehead for invaluable assistance in the bacteriologic work.

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SINGLE INJECTION TREATMENT OF GONORRHEA WITH POTASSIUM PENICILLIN SUSPENSION IN OIL-CONTAINING EPINEPHRINE

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EVER since the effectiveness of penicillin therapy of gonorrhea, by repeated administration of aqueous solutions of the drug was established in 1943,^{6,7} numerous attempts have been made to reduce the treatment to a single injection.⁹ Various vehicles known to prolong the duration of penicillin effect have been used for this purpose.^{4,10} The water-in-oil emulsion proposed by Freund and Thomson⁵ gave, in our experience¹ satisfactory therapeutic results as did the beeswax-in-oil mixture according to Romansky.¹¹

These preparations have, however, a certain number of shortcomings for the practitioner. The beeswax mixture is thick and becomes a resinous uninjectable mass if any moisture reaches it. The beeswax occasionally produces foreign body reactions and local abscesses.¹¹ The practical disadvantage of the material previously studied by us, *i. e.*, the penicillin water-in-oil emulsion, is that the emulsification process has to be done by the physician himself, with sterile materials, and the emulsion requires refrigeration.

The mixture used in the present clinical investigation proved satisfactory in overcoming the disadvantages of the preceding preparations. It consists in a suspension of crystalline penicillin-in-oil containing epinephrine. It is stable at room temperature and after brief shaking of the ampoule is ready for aspiration and injection: it flows readily. The data relating to the prolongation of blood levels in animals and man were presented by Ercoli,

Hueper, Landis, Queally and Schwartz.³ We treated a total of 300 cases of male gonorrhea with this preparation. The therapeutic results are reported in this communication.*

I. DIAGNOSIS, TREATMENT and DETERMINATION OF CURE. The cases treated were 300 consecutive male ambulatory patients with acute gonococcal infections. The diagnosis was established by routine bacteriologic examinations of urethral smears and cultures. The preparation was injected intramuscularly into the buttocks or subcutaneously into the upper outer quadrant of the gluteal region. For the major portion of the investigation an ampoule containing 300,000 units of potassium penicillin and 0.3 mg. of epinephrine in 1 cc. of a vegetable oil was used. The doses injected varied between 0.25, 0.5 and 1 cc. Only exceptionally were 2 cc. doses used.

The criteria of cure were the following: (1) the absence of urethral discharge; (2) clear urine in the "2 glass" tests; (3) at least 2 negative cultures of both urethral and prostatic secretions during a period of at least 2 weeks (37 cases). In the majority of the cases followed up completely (117 out of 154), 3 prostatic cultures were taken during a period of 3 weeks. Peizer's medium was used for cultures; the identification of gonococcus was confirmed in each case by sugar fermentation tests.

II. THERAPEUTIC RESULTS. Out of 300 patients injected with various doses

* The material used in this study was made available to us by the courtesy of Warner Institute for Therapeutic Research, New York, N. Y.

of the preparation investigated, a total of 154 could be followed up for 2 to 3 weeks, for the final determination of cure. The remaining 146 cases were delinquent (48.7%). The results of treatment with different dosage are given in Table 1.

tration of 0.25 cc. per 75,000 units dose was successfully treated with 0.5 cc. per 150,000 units, given by single injection. (The last case of relapse following the 75,000 unit treatment was delinquent.)

After probable cure and admitted sex

TABLE 1.—SINGLE INJECTION TREATMENT OF GONORRHEA WITH A SUSPENSION OF PENICILLIN IN OIL CONTAINING EPINEPHRINE

Volume injected (cc.)	Epinephrine (mg.)	Penicillin (Oxford units)	No. cases	No. cured	No. failed
<i>Intramuscular Administration</i>					
0 25	0 06-0 15	75,000	2	1	1
0 50	0 15-0 50	150,000	45	44	1
1 00	0 1	200,000	19	19	0
1 00	0 3	300,000	7	7	0
2 00	0 6	600,000	4	4	0
<i>Subcutaneous Administration</i>					
0 25	0 06-0 15	75,000	7	6	1
0 50	0 15 0 50	150,000	54	52	2
1 00	0 25 0 30	300,000	11	11	0
2 00	0 60-2 00	600,000	5	5	0
Grand total	154	149	5

It appears that a single injection of 0.5 cc. of the oily suspension, containing 150,000 units of penicillin and 0.15 mg. of epinephrine is sufficient to cure gonorrhea infection in the male. The bacteriologic and clinical examination of 100 patients so treated and followed up for 2 to 3 weeks indicated a cure rate of 97%. Two of the 3 cases which relapsed showed transitory negative bacteriologic findings for a period of 24 hours and relapsed soon thereafter. Since these patients definitely denied any exposure, a diagnosis of relapse was made.

A single injection with 0.25 cc. of the suspension containing 75,000 units and 0.075 to 0.15 mg. of epinephrine cured 7 out of 9 patients. In spite of the small number of patients in this group, it is justifiable to conclude that this dose is insufficient for therapy. A single injection with 1 or 2 cc. of the suspension containing from 200,000 to 600,000 units cured all 46 cases followed up.

It is noteworthy that 3 cases which relapsed following treatment with 0.5 cc. per 150,000 units dose responded promptly to a second injection of the same dose. One case of relapse following the adminis-

tration, 9 cases were diagnosed as reinfections. Five of these cases were re-treated with the original dose used, *i. e.*, 0.5 cc. per 150,000 units in 4 cases and 1 cc. per 200,000 units in the fifth case. All these patients were promptly cured. The 4 remaining cases were delinquent.

Immediate reaction to intramuscular injections of the suspension were similar to those observed when aqueous penicillin solutions are injected. They consist chiefly of a transient burning painful sensation which began about 20 seconds after the injection and lasted for about 2 to 3 minutes. Sometimes it radiated downwards, to subside gradually within 5 minutes. Subcutaneous injection produced no radiating pain, but in some cases a transitory 2 to 3 minutes' painful burning sensation was felt. The site of injection was examined repeatedly during the course of the follow-up period and no local infiltration or other abnormalities were found except in 2 patients who developed 3 cm. subcutaneous indurations which lasted for about 28 days. One of these patients was treated with a very high dose of epinephrine; 2 mg. in 2 cc.

Among 15 patients whose blood pres-

tures were taken before and after the administration of varying amounts of the mixture containing epinephrine, 8 showed no rise or fall in blood pressure. Six patients showed a drop up to 16 mm. of mercury within 15 minutes of the injection and 1 a rise of the blood pressure up to 14 mm. of mercury. Thus, there was no significant effect on the blood pressure. There was no rise in the pulse rate. There were 2 cases which showed exacerbations of a preëxisting dermatophytosis and *Tinea cruris*.

Discussion. The foregoing observations indicate that the minimal effective dose for the treatment of gonorrhea by single injection with a preparation of penicillin in an oily suspension containing vasoconstrictor, consists of 0.5 cc. of the oily suspension containing 150,000 units of crystalline penicillin and 0.15 mg. of epinephrine. A cure rate of 97% followed this dosage. A second injection with the same dosage likewise cured the 3 relapsing cases. There were no relapses in the 46 cases treated with doses higher than 150,000 units.

Our present results of therapy compare favorably with those following the administration of 150,000 units of penicillin in 4.5 cc. of a water-in-oil emulsion (cure rate 96.2%)¹ and with multiple injections of penicillin in aqueous solution (cure rate, 96.5 to 100%).²

The prolongation of the penicillin effect by using epinephrine-in-oil as a vehicle for penicillin³ is probably responsible for the excellent therapeutic results. Comparing our clinical findings with the figures on blood levels given by Ercoli, Hueper,

Landis, Queally and Schwartz, it would seem that the therapeutic dose of 150,000 units yields detectable amounts of penicillin in the serum of the patient for a period of approximately 12 hours. The observation that the relapses are as sensitive to treatment as the initial infection cannot be explained in the light of our present knowledge. It indicated, in any event, that the relapse strain is certainly not becoming resistant to penicillin. This observation limited to a small, statistically insignificant number of cases deserves further study for its broader significance of the relation of penicillin effect upon a relapsing infection.

Summary and Conclusions. 1. This study was directed toward the evaluation of a single injection treatment of gonorrhea with a suspension of potassium penicillin in oil containing epinephrine.

2. Single injections of 150,000 units intramuscularly or subcutaneously, in a total volume of 0.5 cc. cured 97 of 100 patients. The 3 patients who did not respond to the initial injection were promptly cured with a second injection of an identical amount of penicillin.

3. All of 19 patients who were treated with 200,000 units in 1 cc. intramuscularly were cured. Likewise all of 18 patients treated with 300,000 units in 1 cc. and all of 9 patients treated with 600,000 units in a total volume of 2 cc. responded to this form of therapy.

4. No untoward local or systemic reactions were observed following the subcutaneous or intramuscular injection of the suspension of crystalline potassium penicillin in oil with epinephrine.

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THE EFFECTIVENESS OF PENICILLIN IN THE TREATMENT OF NASOPHARYNGEAL DIPHtheria

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THE early investigation of penicillin for clinical use revealed its effectiveness against the *Corynebacterium diphtheriae*. The efficacy of penicillin in the treatment of diphtheria has not been as fully studied as in other diseases. Furthermore, controversy still exists concerning the clinical value of penicillin in diphtheria. The comparative paucity of clinical material has been partly responsible; the presence of the diphtheria toxin has also complicated the problem.

This paper deals only with the management of the early case of nasopharyngeal diphtheria. From the data presented, it is thought that some conclusions can be drawn regarding the efficacy of penicillin treatment. It must be realized that all the patients studied had been previously immunized according to the prescribed Army Schedule.¹⁰ Initial immunization had been completed on all cases included, but the dates thereof and the dates of "booster" injections are not known.

Procedure. The case material was collected over an 8 month period, from September 1946 to May 1947. The patients in this series were young men in the United States Army occupation forces deployed in the general area surrounding Frankfurt a/M, Germany. The hospital in which the patients were studied was the 97th General Hospital located in Frankfurt.

Diagnosis. All cases diagnosed as diphtheria (nasopharyngeal) had the usual history of acute sore throat, though varying greatly in intensity. General malaise and systemic complaints were usually present. The physical examinations revealed evidence of nasopharyngitis. Briefly, there was usually erythema and congestion of nasal passages. The pharynx, palate, tonsils, if present, and surrounding tissues showed erythema and edema. The close-fitting,

smooth, gray membrane described as typical of diphtheria was seldom seen. Every case herein reported, however, had a positive nasal and/or pharyngeal culture for *Corynebacterium diphtheriae*; and further, each culture reported positive and included in this series had a confirmed positive virulence test. The severity of the physical findings could not be correlated with positive diphtheria culture reports, since many patients had a coincident follicular or parenchymatous tonsillitis.

Bacteriology. Bacteriologic identification of the corynebacterium was done routinely by the laboratory. The standard media and identification procedures in use throughout Army laboratories were employed here.

Every culture positively identified was forwarded to the United States Army 4th Medical Laboratory. Here virulence studies were done under standard technique employing guinea pigs. As mentioned above, only those cases giving positive virulence studies are included.

Summary Card. To simplify the following of patients and assembling data, summary cards were used. These had been in use by the medical service at the hospital for some time previous to this study. Since they proved to be of much value, a sample is shown in Figure 1.

A total of 139 cases are presented; 88 of these received the "routine" treatment; 51 received the "routine" treatment plus "penicillin early."

Type of Treatment. (a) By "routine treatment" is meant the following: Bed rest, nursing care, necessary sedation and analgesia, special diets and the usual general medical measures. The specific or local treatment consisted of mouth washes and gargles prepared of warm water, saline and occasionally peroxide. Every case received diphtheria antitoxin 100,000 units intramuscularly. The antitoxin was given in each instance as soon as a positive culture for

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corynebacterium was reported. In some instances the antitoxin was given before the culture report was received. The report of the virulence test was not awaited before giving the antitoxin because of the additional time interval involved. In the great majority of the patients sulfadiazine had been used before a diagnosis of diphtheria was established. Exact figures on the number of patients receiving sulfadiazine are not known, since the special reference cards did not always include that information. However, the distribution of patients treated with sulfadiazine is approximately equal in both groups. No penicillin was given as a routine measure, either locally or systemically.

2 days, and at 4 weeks plus 4 days. If the last 3 cultures taken were negative, the patient was considered no longer a carrier and was transferred for convalescence or discharge. If any of the cultures following the original one were positive, the patient received further treatment as outlined below. Following this second positive report, again a period of 2 weeks elapsed before the series of 3 cultures 2 days apart was repeated for clearance.

Results. (a) *Routine Treatment.* Of the 88 cases treated according to the "routine" method, 46 showed a positive culture at the first 2 week interval; 35 cases showed a negative culture at the

FIG. 1.—SAMPLE PATIENTS' SUMMARY CARD OF CLINICAL DATA

NAME	Date of 1st positive culture	Dates for future cultures	Electrocardiogram	Treatment	Remarks	Type of organism
.....	14 Jan. N/P —neg./pos.		14 Jan. —normal	Penicillin, 20,000 u. q. 3 hrs. 14 Jan.—20 Jan.		Gravis
.....		28 Jan. N/P —neg.	21 Jan. —normal		Up and about	
.....		11 Feb. N/P —neg.	28 Jan. —normal			
.....		13 Feb. N/P —neg.			No complaints	Gravis
.....		15 Feb. N/P —neg./ pos.	15 Feb. —T wave change	Tonsillectomy, 17 Feb.		
.....			22 Feb. —normal	Penicillin, 20,000 u. q. 3 hrs. 16–18 Feb.		
.....		1 Mar. N/P —neg.	1 Mar. —normal		Up and about	
.....		3 Mar. N/P —neg.			No complaints	
.....		5 Mar. N/P —neg.			Discharged	
.....						
.....						

N—nasal culture. P—pharyngeal culture.

(b) By routine plus "penicillin early" is meant the following: All the measures mentioned above were included; but in addition the patient received penicillin intramuscularly. This drug was not used locally. And it should be noted that the penicillin was begun at the first report (bacteriologically) of a positive culture for corynebacterium. These reports were usually available within 4 days. The penicillin was given intramuscularly, 20,000 units every 3 hours. This was continued for 50 doses or 1 million units, unless otherwise stated. This dosage was arrived at empirically and with the advice of others studying the problem.

Treatment Schedule. Following a positive culture report for *C. diphtheriae*, the patient was transferred to the isolation section. Cultures of the nose and throat were then taken at an interval of 2 weeks from the original positive culture, at 4 weeks, at 4 weeks plus

2 week interval; 7 additional cases treated in the routine manner, negative at the 2 week period, later were shown to be in a carrier state by a positive culture appearing in the clearance series. Thus a total of 53 cases (60%) developed a carrier state as opposed to the 35 (40%) who did not.

(b) *Penicillin Early.* Of the 51 cases who received the routine plus "early" penicillin treatment, 43 had negative cultures at the 2 week interval and 8 were positive. Of the 43, only 3 who were negative at 2 weeks, later became positive and required further treatment. The (79%), with permanently negative cultures as opposed to 11 positive cases (21%) is obviously a better result than that of those getting "routine treatment."

It may be mentioned here that the 2 week culture seems to be of considerable value as an aid to recognizing the possible development of the chronic carrier state. This is supported by the fact that only 10 (13%) of the 75 cases negative at 2 weeks, later became positive. In other words, prognosis regarding the absence of the carrier state is nearly 90% correct when based on the 2 week culture alone. This figure becomes even higher when the "early" penicillin group is considered alone. As mentioned, only 3 out of 43 cases first negative later became positive. This is less than 7% error.

Further evaluation of the above is not possible because the patients reported positive at the 2 week interval were put on intensified treatment programs immediately. This was done to shorten the period of hospitalization necessary.

(c) *Hospitalization Time.* A comparative study of the required time for hospitalization between the 2 series is of interest (Table 1). The average time of hospitalization for patients with a negative 2 week culture was 35 days; and the average time of hospitalization with a positive 2 week culture was 50.3 days. These figures for average hospitalization include patients who became negative without further treatment after a 2 week positive culture. They do not include some of those patients held beyond 50 days for recovery from complicating carditis. These patients had positive cultures at the 2 week interval. Consequently the 50 day figure is in error on the low side only. This difference in average hospitalization is also significant. These data give additional support to the value of the 2 week culture.

(d) *Penicillin Late.* In contrast to the results with penicillin given early, the late use of penicillin intramuscularly was not so successful; 40 cases of the positive 2 week group (53) treated routinely on admission, received penicillin only when the 2 week culture had been reported positive. They received 1 million units of penicillin intramuscularly, 50 doses of 20,000 units

at 3 hour intervals. Of these 40 cases, 16 showed negative cultures (40%), while 24 (60%) remained positive. Several of these 24 cases received penicillin in the dosage above a second time. None was successfully cleared of the carrier state until tonsillectomies were performed.

COMPLICATIONS. There were no serious complications seen in this series. The most frequent postdiphtheritic damage found was a carditis diagnosed only by the electrocardiogram. Of the "routine" and penicillin "early" cases responding with a negative culture series, the percentage showing carditis beyond the first 2 weeks was approximately the same; namely, 42% for the former and 40% for the latter.

Of the unsuccessful group treated routinely, that is, those positive at 2 weeks, 19 of 54 cases (35.2%) showed a carditis. Certainly from this point of view penicillin cannot be said to have helped. However, of the group who underwent tonsillectomies, following penicillin at 2 weeks to clear the carrier state, 50% showed continuing electrocardiographic changes for more than 4 weeks. The other 2 groups mentioned above (those with negative 2 week cultures) each showed only 30% having electrocardiographic changes longer than 4 weeks.

The same group undergoing tonsillectomies had the longest average hospitalization of over 61 days. This suggests that the longer an organism remains in the throat, the greater its chance of doing damage as manifested in this series by continuing changes in the electrocardiogram.

Discussion. It was interesting to find that the majority of cases harbored the gravis strain. This was almost universally true until November 1946. From that time on, a gradually increasing proportion showed the mitis strain. By March 1947 over 50% of cases were of mitis etiology. There was no significant difference found in the incidence of complications when cases due to the mitis strain were compared to cases due to the gravis strain.

**A CLINICAL EVALUATION IN CHILDREN OF THE TOXICITY AND EFFICACY OF
CARONAMIDE (4-CARBOXYPHENYLMETHANESULFONANILIDE) FOR THE
COMPETITIVE INHIBITION OF PENICILLIN EXCRETION***

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In recent publications by Beyer and his co-workers¹ it was demonstrated that caronamide (4-carboxyphenylmethanesulfon-anilide) administered orally, by inhibiting the rapid renal excretion of penicillin, was capable of maintaining higher and more sustained levels of penicillin than normally occurred after a given dose. In this research there is presented an evaluation of the toxicity of caronamide in children and of its efficacy in increasing the plasma concentration of orally administered penicillin.

Penicillin is lost rapidly from the body fluids because of its rapid renal elimination. It has been shown that penicillin is excreted by the kidney in the same manner as is p-aminohippuric acid (PAH). Since PAH at low blood concentrations is almost completely extracted from renal arterial blood in one circulation through the kidneys, it follows that the amount of PAH appearing in the urine per minute is practically equal to the quantity of PAH contained in the volume of plasma circulating through the kidney per minute. Thus the renal clearance for PAH and penicillin (*i. e.* the quantity of plasma from which these substances are completely removed in one minute by the kidney) is

a measure of the renal plasma flow per minute.² The renal clearance of penicillin is accomplished by a combination of glomerular filtration and tubular excretion. Since this clearance approximates the renal plasma flow and since in man 20% of the renal plasma flow is filtered at the glomerulus (the so-called filtration fraction) the greater part (80%) of urinary penicillin is excreted by the tubules.

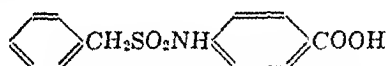
Caronamide decreases the rapid renal excretion of penicillin by its inhibitory action on the tubular excretory mechanism for penicillin. This inhibition is effected by halting the tubular transport mechanism involved, without caronamide itself being excreted by the tubules and without inhibiting other tubular transport mechanisms.³ This compound is eliminated essentially by glomerular filtration. The inhibitory effect of caronamide on the tubular transport mechanism is analogous to the *in vitro* competitive inhibition of the action of an enzyme on its substrate by another compound possessing an affinity for, but being refractory to, the action of the enzyme.

The mode of action of caronamide may be contrasted with the inhibition of penicillin excretion by Diodrast or PAH

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(p-aminohippurate), which are excreted by the same mechanism as is penicillin.⁸ These latter agents do not suppress the function of that common transport system but in being excreted by it limit its functional capacity to excrete penicillin on a "mass action" basis. The rapid tubular excretion of PAH and Diodrast, together with the necessity for the parenteral administration of either agent, make their use for this purpose impractical in ordinary penicillin therapy. Caronamide, because it is excreted only by glomerular filtration, is eliminated at a relatively slower rate and may be administered orally.

The compound caronamide was described by Sprague, Ziegler, Miller and Cragoe.¹⁰ It has the following chemical structure:



Beyer¹ has reported this agent (1) to fulfill the original physiologic limitations imposed by the concept of its mode of action; (2) to be markedly effective in dogs in inhibiting the renal tubular elimination of penicillin at moderate dosages and in a reversible manner; (3) to enhance from 4- to 16-fold the chemotherapeutic effect of penicillin in experimental pneumococcic and typhoid infections in mice;* and (4) to have low order or toxicity in the mouse, rat, rabbit, dog and monkey.

TOXICITY STUDIES. Three groups of 6 patients each were selected from the orthopedic and medical services of the Children's Hospital of Philadelphia for this phase of the work. These children constituted a heterogeneous group from the standpoint of diagnosis and present medical histories. Fifteen patients were studied; three of them were used in both the first and third group. Ages ranged from 2 to 13 years and weight from 21 to 100 pounds (9.5 to 45.5 kg.).

Transposing from the experimentation on dogs, it was anticipated that an effective dosage of the compound would be

about 0.2 gm./kg./24 hours. Consequently the 3 groups of patients were given total caronamide dosages of 0.1, 0.2 and 0.4 gm./kg./day, divided into equal aliquots and administered at intervals of 4 hours, day and night. The duration of each group study was at least 7 days. Before beginning each study, 24-hour urine collections and fasting blood samples for chemical and hematologic examination were obtained from each patient. Chemical and hematologic analyses were performed again after the first 3 or 4 days of drug administration and finally at the termination of the experiment.

A systematic daily record, except for hematology and chemistry, wherein the following data were recorded, was kept for each patient: subjective and objective manifestations of toxicity such as nausea, vomiting, rash; daily temperature range; appetite; weight; 24-hour fluid intake and output; and blood pressure. In addition the following data were obtained: total erythrocyte and leukocyte counts; differential white cell counts; hemoglobin; blood urea, glucose, N.P.N.; urine casts, crystals, microscopic hematuria, proteinuria, reducing substances, total nitrogen, Gmelin's test for bile pigments, specific gravity, and pH.

The course of events was such that the group receiving the 0.1 gm./kg./day dosage was started first. No patient was given less than 3 gm. per day, 0.5 gm. every 4 hours, even if the calculated dose was less than this amount. After 3 days wherein no sign of drug tolerance was evident, the second group was started on a dosage of 0.2 gm./kg./day. After 4 days, the third group was begun, and this included 3 children from the first group whose medication was interrupted for only 2 days. The daily dosage for this group was 0.4 gm./kg./day. Administration of the drug to 3 children in this group was stopped at the end of one week, but the others were allowed to continue taking it

* Detailed evidence in support of this statement is given in an article by Verwey and Miller (*Proc. Soc. Exp. Biol. and Med.*, 65, 222, 1947).

for a second week. Since the drug was available in 0.5 gm. tablets, in the case of the smaller children, they usually were mashed in a spoon and administered with orange, cherry, or strawberry syrup.

RESULTS. There were no manifestations of toxicity that necessitated withdrawal of caronamide from any of these 15 patients or the next group of 5 that received penicillin plus the drug. The patients tolerated the caronamide well. There was only one instance of vomiting of the tablets from day to day, and that was in a patient who had tolerated 6 gm. per day but who vomited frequently when given 18 gm. per day as a member of the third group. Other isolated instances of vomiting were attributable to giving the tablets without water, to a meal that the child disliked, or to other similar secondary causes.

There were 2 isolated instances of crystalluria among the repeated urinalyses on each patient. These occurred in the second group (0.2 gm./kg./day) and at a urinary pH of 5.9 and 6.1 respectively in the 2 patients. These 2 children received 5 and 5.5 gm. of the drug per day. The crystals were clustered as sheaves. There seems reason to believe that the development of crystalluria was dependent on the pH of the urine, since it was not encountered at pH values above 6.2. However, there were 9 instances in which the urinary pH was below 6.2, in one case 5.9, where crystalluria was absent. No attempt was made in this study to avoid or attempt to correct these transient findings. The crystallurias were not accompanied by gross or microscopic hematuria or by casts.

There were no changes in hematologic findings or persistent elevation of temperature attributable to the drug. To be sure, temperature and leukocyte count increased following an intercurrent pharyngitis, the development of a wound infection, and following a smallpox vaccination. The criterion of a drug fever was taken as an otherwise unexplained elevation of rectal temperature to over 100° F. on at least 2

successive days any time during caronamide administration.

There were 3 instances of the appearance of a rash during or immediately following the administration of the drug. No 2 cases were alike in the nature or distribution of the rash. The first occurred on the fourth day of drug administration, the patient being in the first group (0.1 gm./kg./day). This rash consisted of small erythematous, grouped papules limited to the extensor surfaces of both wrists and was preceded by itching several days prior to the appearance of the rash. This child began to use crutches with leather arm straps that were in constant moving contact with the wrists and it was felt that the rash represented a contact dermatitis rather than a drug reaction. Only traces of the rash could be made out at the termination of the experiment 3 days later. On the fifth day a second patient in the third group (0.4 gm./kg./day) developed a moderate maculo-papulo-vesicular rash on the lower portions of the legs and feet, including the soles. There were a few lesions on the lower portions of her arms. This faded almost entirely within 24 hours. In both of these instances the lesions faded despite the continued administration of the drug.

The third case occurred in the patient in the third group previously mentioned as having vomited frequently. She developed a florid small macular rash over her face, neck, arms and chest 24 hours after the termination of drug administration, which was accompanied by a mild palpebral conjunctivitis and a mild leukocytosis. There was no adenopathy. The rash faded completely within 48 hours after its appearance. All 3 children who manifested these dissimilar rashes were convalescent cases of poliomyelitis.

Another interesting observation was the appearance of reducing substance in the urine of 3 patients in the third group, one of them being the patient described as having a rash 24 hours after discontinuation of the drug. In this case and in another the reducing substance was pres-

ent on only one occasion, but in a third patient it was present consistently during drug administration.

This reducing substance was not glucose, nor was there any change in the blood glucose level at the time of its appearance or later. Instead, it appeared to be a pentose. In each instance where a qualitative test for urinary reducing substance was positive (Benedict's Test) it was also estimated quantitatively. A similar amount of glucose was added to normal urine and aliquots of both specimens were yeasted to remove fermentable substances. Following yeasting, the control urines were negative whereas the test samples still contained their initial concentration of reducing substance. Tests for glucuronates were negative. Lactose was not the non-fermentable substance. The case records for medication, diet, etc., were irrelevant.

It is probable that these were instances of pentosuria. One case of pentosuria (if such it was) occurred only at the time of a pharyngitis in a convalescent poliomyelitis patient. Another occurred following vaccination against smallpox of a patient having congenital malformation of the joints. The pentosuria was associated with an elevation of temperature. In the third case the pentosuria was only detected on the last day of the drug administration, 24 hours before the appearance of a rash. It is quite possible that the pentosuria was precipitated by the drug under conditions of metabolic stress in patients undergoing some abnormal pattern of muscular or joint metabolism. A certain amount of credence may be lent this interpretation since pentosuria only occurred in post-poliomyelitic cases with the exception of 1 case, involving congenital malformations of the joints necessitating the patient's legs being in a cast.

This finding recalls the observation of Dr. A. S. Minot that patients having progressive muscular dystrophy have pentosuria.⁷ In contrast to this explanation

was the report by Beyer, McKinney, and Tillson that young dogs given 1 to 1.5 gm. of caronamide/kg./day on an identical 4-hour dosage régime developed pentosuria. Dogs given smaller daily dosages of the drug did not manifest pentosuria.^{4c}

The occurrence of non-fermentable reducing substance in the urine has been the first and usually the only characteristic systemic effect of the drug. The pentosuria was reversible by withdrawal of the agent, and its continued occurrence seemed of little consequence in either our patients or in the dogs referred to above.

In general there were no effects attributable to drug reaction that have not been noted in the foregoing discussion.

The Effect of Caronamide on Renal Function and the Blood Level Response to Penicillin Administered Orally. The design of these experiments was as follows: Five patients were selected for the study. On successive days before administration of penicillin and caronamide renal function tests were performed on each patient. These included measurements of the glomerular filtration rate (manitol clearance), minimal renal plasma flow (PAH clearance at low plasma levels), maximal ability of the tubules to reabsorb glucose (glucose T_m) and the maximal capacity of the tubules to excrete p-amino hippurate (PAH T_m).

Following the renal function test the first penicillin control phase wherein each patient was given orally 100,000 units of crystalline sodium penicillin-G* dissolved in water immediately before administration and flavored with a fruit syrup was begun. The dosage was repeated every 4 hours day and night. Each morning the 9 A.M. dose was given by one of us (other dosages were administered by the nursing staff). Breakfast was withheld until a blood sample was drawn exactly 1 hour after the drug was given.

The duration of the first control phase was 4 days. The schedule was so arranged

* The sodium salt of crystalline penicillin-G used in this work is thought to be at least 90% pure. It was obtained from the Commercial Solvents Corp., Terre Haute, Ind.

that during this period one 4-hour penicillin dose—plasma concentration response curve was taken on each patient. These were always started after the 9 A.M. dosage and all food was withheld until after the last or 4-hour blood sample was taken for penicillin assay. Thereafter, at 1 P.M., the next penicillin dose and lunch were given the patients.

Since 10 cc. samples of citrated blood were desired for the Rammelkamp assays, the experiment had to be designed to minimize bleedings and yet obtain a maximal amount of information. Sufficient blood was drawn to permit repetition of an assay when desired. The bloods were chilled immediately and were handled aseptically throughout. The organism used in the assay of the plasma was a hemolytic streptococcus. Human red cells were used in the determination of end points and a half-step dilution system was employed to minimize the percentage error of the assay.⁵ It had been ascertained previously that caronamide did not influence penicillin assays.^{4a} The lower limit of the assays was 0.02 μ /cc.

Immediately following the control period the first drug phase, wherein a daily dosage of 0.2 gm./kg. of caronamide was divided as equally as possible into 6 aliquots, and administered every 4 hours together with 100,000 units of penicillin, was begun. Here again the duration of the test was 4 days, penicillin blood levels were determined daily 1 hour following the 9 A.M. dose, and a 4-hour penicillin blood

level curve was obtained on each patient, once during the period.

Following the initial drug phase the daily dosage of caronamide was doubled (0.4 gm./kg.). Otherwise the protocol was as has been outlined for the first drug phase. After the second 4-day drug period the administration of caronamide was stopped.

The administration of penicillin was continued as a second control phase. Forty-eight hours after the last dose of caronamide and on 2 succeeding days either a 1-hour, or a 4-hour, penicillin blood level curve was obtained on each patient. There were 2 exceptions to the 1-hour bleedings following the 9 A.M. dosage where this would have conflicted with renal function procedures. The renal function tests were repeated on the children during and following this second penicillin control period. The tests on the first child were performed 48 hours after the last dose of caronamide.

Throughout this whole procedure the laboratory and clinical studies, except for chemistry, were carried out periodically as in the toxicity studies. There were no notable changes disclosed by these tests.

Results. The general effect of caronamide on the blood level response to penicillin administered orally has been summarized in Table 1. Herein all the control values and blood levels at both levels of caronamide dosage have been averaged and compared at corresponding time intervals following the 9 A.M. dose of 100,000

TABLE 1.—THE AVERAGE PENICILLIN PLASMA LEVEL RESPONSE OF 5 PATIENTS TO THE ORAL ADMINISTRATION OF THE ANTIBIOTIC AGENT ALONE AND WITH CARONAMIDE

The dosage of penicillin was 100,000 units every 4 hours. The dose of caronamide administered with each dose of penicillin was one-sixth the daily dosage of 0.2 gm./kg./day or of 0.4 gm./kg./day.

Time after dose	Penicillin control (plasma conc. u./cc.)	Penicillin plus caronamide (0.2 gm./kg./day)		Penicillin plus caronamide (0.4 gm./kg./day)	
		Plasma conc. (u./cc.)	Fold increase over control	Plasma conc. (u./cc.)	Fold increase over control
1 hr.	0.325 (28)*	0.507 (20)	1.6	0.916 (20)	2.8
2 hr.	0.082 (10)	0.155 (5)	1.9	0.412 (5)	5.0
3 hr.	0.032 (10)	0.090 (5)	2.8	0.257 (5)	8.0
4 hr.	0.013 (10)	0.026 (5)	2.0	0.188 (5)	14.5

* Number of samples.

units of penicillin, or of penicillin and drug.

Scanning the data in Table 1, it is apparent that the overall effect of the 0.2 gm./kg./day dosage was to increase the penicillin plasma concentration 1.8- to 2.8-

fold over the control values. The 0.4 gm./kg./day dosage of caronamide further increased the antibiotic blood level from 2.8- to 14.5-fold. Whereas the response at the lower dosage of caronamide was fairly

TABLE 2.—THE AVERAGE ANTIBIOTIC PLASMA LEVEL FOR INDIVIDUAL PATIENTS ONE HOUR FOLLOWING THE ORAL ADMINISTRATION OF PENICILLIN ALONE AND WITH CARONAMIDE

The dosage of penicillin was 100,000 units every 4 hours. The dose of caronamide was one-sixth of the total daily dosage (0.2 gm./kg./day or 0.4 gm./kg./day) administered every 4 hours with penicillin.

Patient	Penicillin control (u./cc.)	Plus 0.2 gm. caronamide (u./cc.)	Fold increase over control	Plus 0.4 gm. caronamide (u./cc.)	Fold increase over control
M. T.	0 430 (6)*	0 529 (4)	1 2	0 899 (4)	2 1
O. L.	0 282 (5)	0 321 (4)	1 1	0 600 (4)	2 1
J. Sl.	0 387 (6)	0 599 (4)	1 6	0 771 (4)	2 0
J. Su.	0 321 (6)	0 499 (4)	1 6	1 453 (4)	4 5
M. A.	0 205 (5)	0 586 (4)	2 9	0 858 (4)	4 2

* Number of samples.

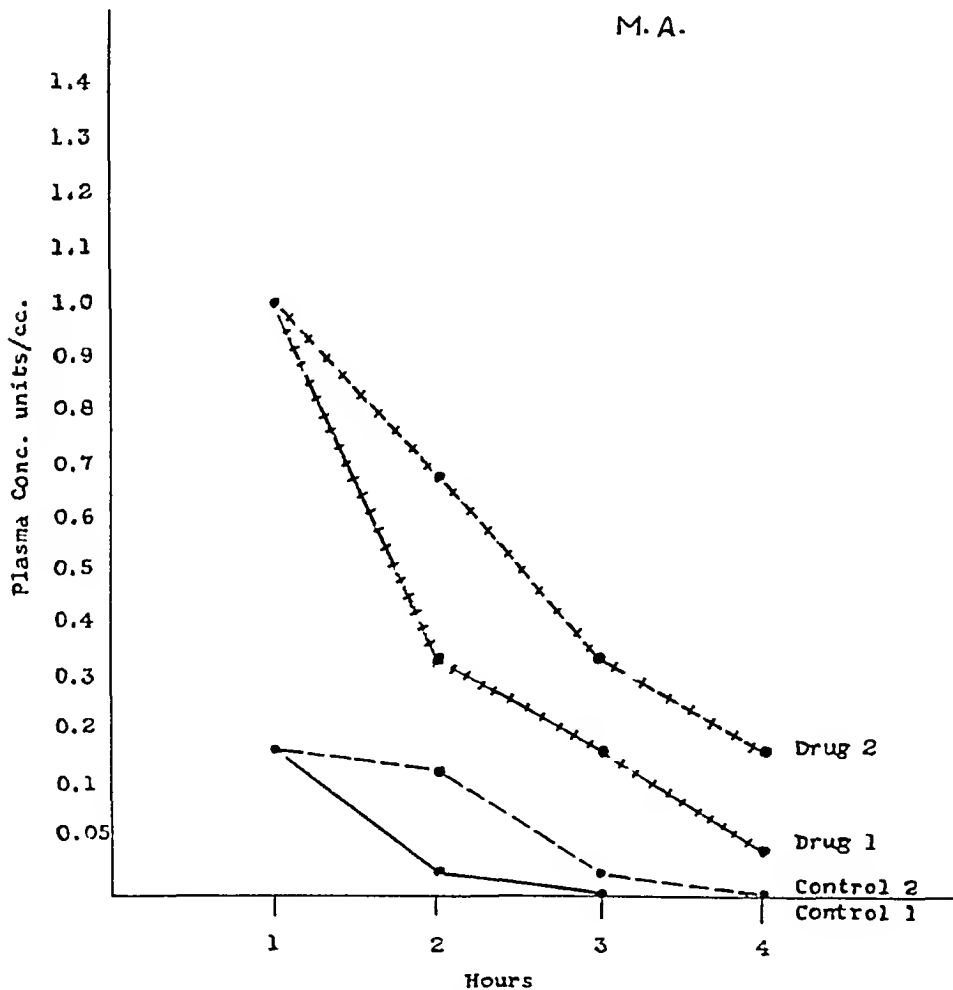


FIG. 1.—Patient M. A.: The effect of caronamide on the 4-hour antibiotic plasma level following the administration of 100,000 units of penicillin orally. C. 1 and C. 2 were two control curves wherein penicillin was administered alone. The actual dose of caronamide was given orally with penicillin 1 hour before lower drug curve was 0.5 gm. Similarly, the dose of caronamide for the top drug curve was 1 gm.

uniform at all points in the 4-hour curve there was an incommensurate increase in its effect in the latter part of the 4-hour curve at the higher dosage. It is interesting that the effect on 1-hour plasma concentrations increased fairly uniformly with the increase in caronamide dosage even though the amount of penicillin was held constant. The standard deviation of 1-hour values for the controls was ± 0.37 ; for the lower drug dosage, ± 0.58 ; and for the higher drug dosage ± 0.28 .

The 1-hour values for control and drug phases for each patient have been compared in Table 2. Here the individual increase in antibiotic plasma level 1 hour following the coadministration of penicillin and caronamide was 1.1- to 2.9-fold

for the 0.2 gm./kg./day dosage, and 2- to 4.5-fold for the 0.4 gm./kg./day dosage. This is probably the least favorable comparison of the data that can be made since it assumes a maximal effectiveness of the caronamide coadministration at the height of the absorption of penicillin. From such data one might deduce that ordinarily the preponderant amount of penicillin absorbed is excreted within the first hour. This would seem to be true since actually it is possible with the aid of caronamide to stop the excretion of sufficient penicillin to such an extent that its accumulation in the body amounts to as much as a 4.5-fold increase in antibiotic plasma concentration within 1 hour.

In Figures 1 to 5 are presented the

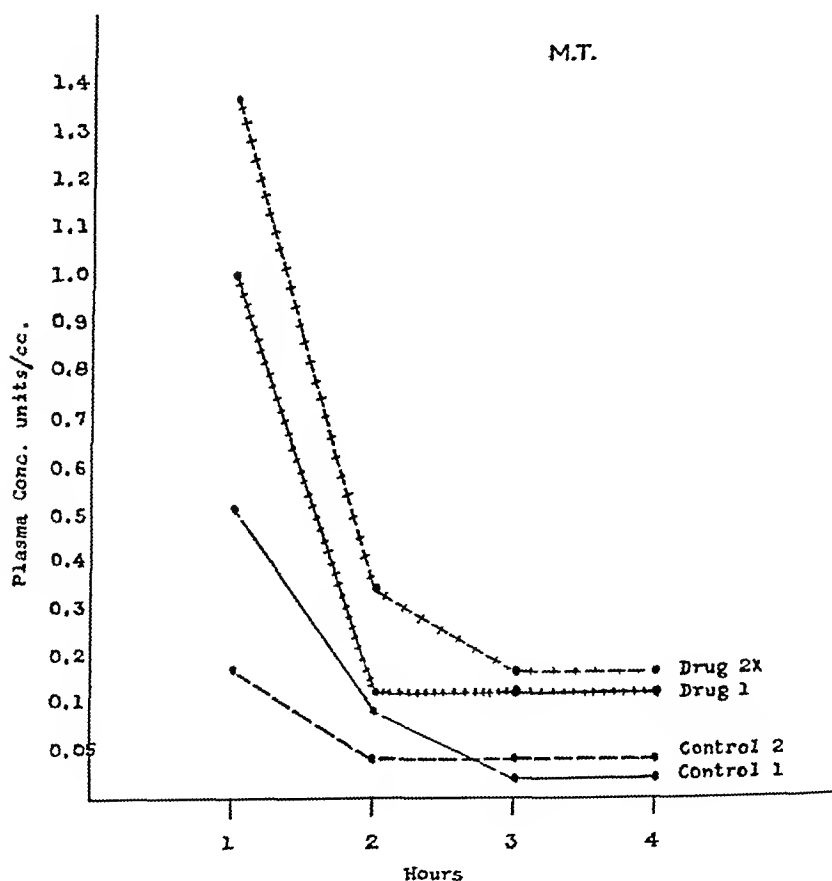


FIG. 2.—Patient M. T.: The effect of caronamide on the 4-hour antibiotic plasma level following the administration of 100,000 units of penicillin orally. C. 1 and C. 2 were two control curves wherein penicillin was administered alone. The actual doses of caronamide given orally with penicillin 1 hour before the lower drug curve was 0.5 gm. Similarly, the dose of caronamide for the top drug curve was 1 gm.

individual 4-hour dose response curves for 5 children. The curves in Figure 6 represent the average control and drug response data for the group of 5 patients. The only noteworthy difference between these data and those presented in Tables 1 and 2 is the lack of a higher initial response following the greater of the 2 caronamide dosages.

The renal function studies before and 48 hours following the eighth day of administration of caronamide are summarized in Table 3. For technical reasons some of the values in both the initial and final determinations appear "out of line." The determinations of renal function on 1 of the children who wore body casts were omitted as being unsatisfactory in both phases. It

seems justifiable to conclude that caronamide did not affect irreversibly glomerular filtration, renal plasma flow, PAH Tm, or glucose Tm, even though we acknowledge the unreliability of some of the absolute values given in Table 3. The magnitude of the data presented in Table 3 is the same as Rapoport and Rubin had found previously to hold for children⁹ and agrees with similar values for adults.⁶ It had been ascertained previously in dogs that, whereas caronamide did decrease the clearance of PAH when the two were administered together, it did not affect glomerular filtration, urea clearance, glucose Tm, arginine Tm, or sulfonamide clearance.¹

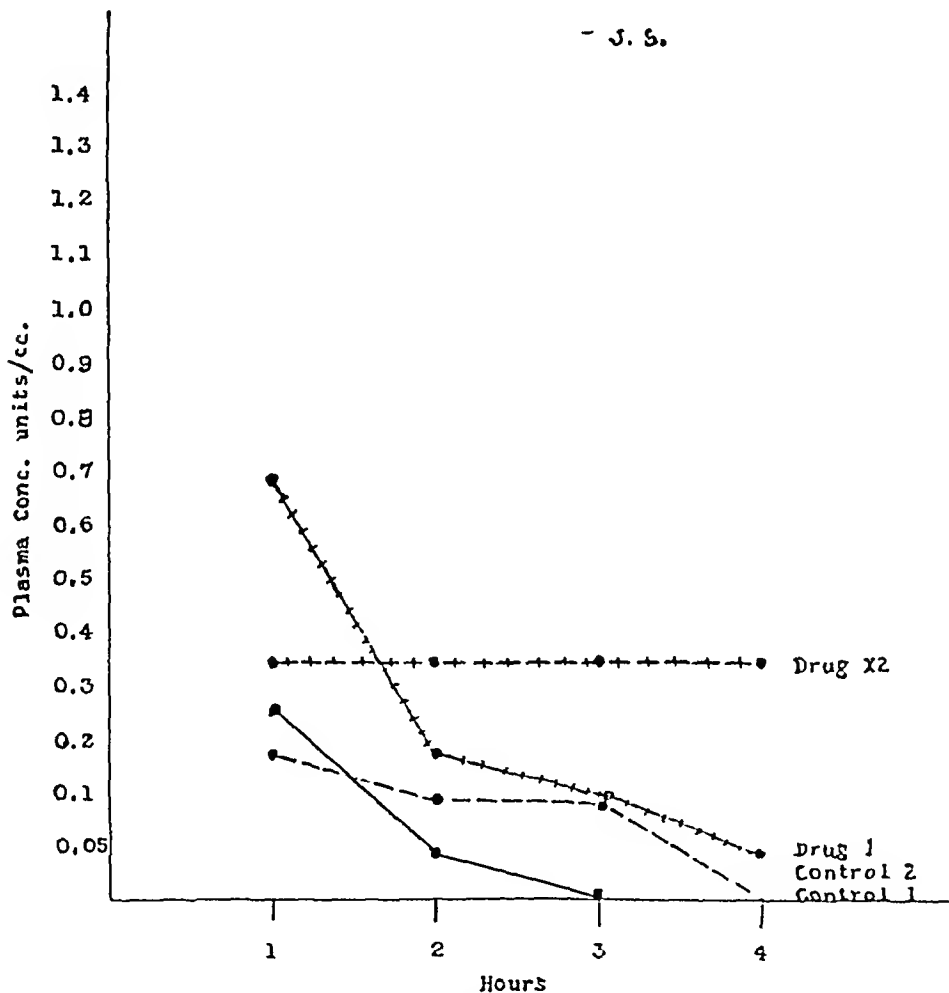


FIG. 3.—Patient J. S.: The effect of caronamide on the 4-hour antibiotic plasma level following the administration of 100,000 units of penicillin orally. C. 1 and C. 2 were two control curves wherein penicillin was administered alone. The actual dose of caronamide given orally with penicillin 1 hour before the lower drug curve was 0.5 gm. Similarly the dose of caronamide for the top drug curve was 1 gm.

TABLE 3.—RENAL FUNCTION STUDIES BEFORE AND FOLLOWING THE ORAL ADMINISTRATION OF CARONAMIDE IN A DOSAGE OF 0.2 TO 0.4 GM./KG./DAY FOR A PERIOD OF 8 DAYS

These values have been corrected to a body surface area of 1.73 sq. m.

	Patients			
	O. L.	M. T.	J. Su.	M. A.
Surface area, sq. m.	0.98	0.85	0.88	0.71
Glomerular filtration rate, cc./min.:				
B*	125	158	111.8	136
A†	160	126.8	94.8	127
Renal plasma flow, cc./min.:				
B	810.7	802	527	609
A	732.8	732	533	638
PAH Tm, mg./min.:				
B	97.9	112	33.5	50.4
A	74.7	76.1	55.4	76
Glucose Tm, mg./min.:				
B	341	288	292	376
A	478	241	329	409

* B = Before therapy (control).

† A = After therapy (drug effect).

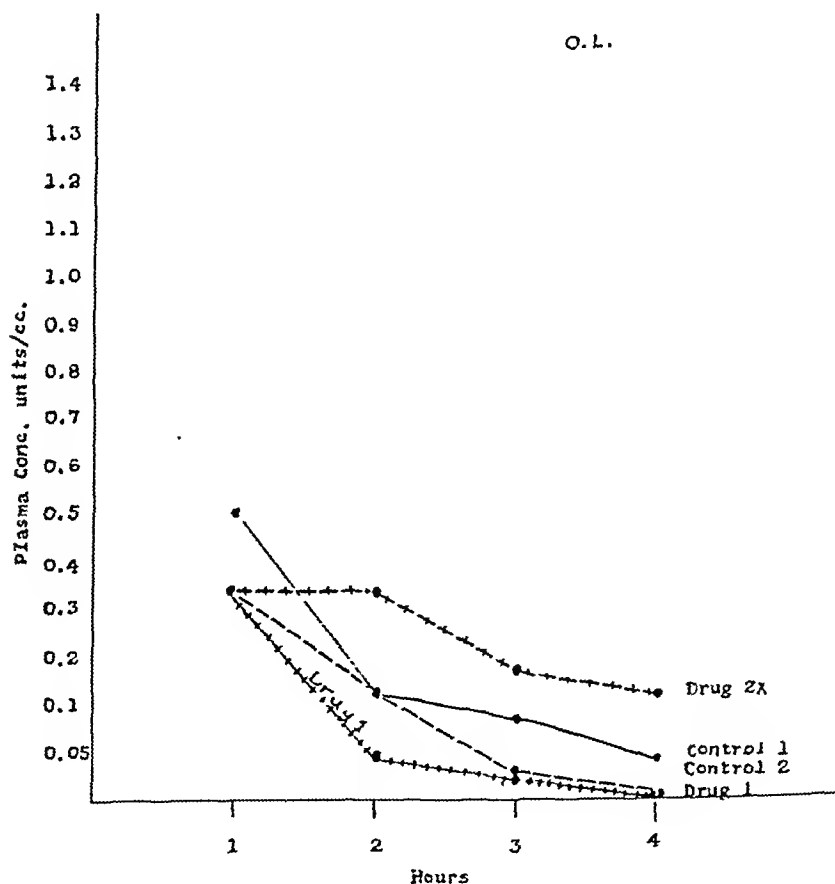


FIG. 4.—Patient O. L.: The effect of caronamide on the 4-hour antibiotic plasma level following the administration of 100,000 units of penicillin orally. C. 1 and C. 2 were two control curves wherein penicillin was administered alone. The actual dose of caronamide given orally with penicillin 1 hour before the lower drug curve was 0.5 gm. Similarly, the dose of caronamide for the top drug curve was 1 gm.

Summary. When tested in children, the oral administration of caronamide at a dosage of 0.2 gm./kg./day together with penicillin increased the antibiotic plasma concentration 1.8- to 2.8-fold over the control values when penicillin was administered alone. When the dosage of caronamide was increased to 0.4 gm./kg./day the penicillin plasma concentration was increased 2.8- to 14.5-fold over the control figures.

There was no instance of toxicity in these patients that warranted discontinuance of caronamide when the compound was administered in oral dosages of 0.1 to 0.4 gm./kg./day over a period of 1 or 2 weeks. Although there were 2 urine specimens that contained drug crystals and 3

instances of rash, in which no 2 cases were similar in appearance or distribution, these did not require special attention. Two of the rashes cleared up during continued administration of drug and the third appeared 24 hours after the drug had ceased to be given. There were 3 cases in which one or more isolated instances of "pentosuria" were found, and these were associated with a pharyngitis, smallpox vaccination, or the rash that appeared after the drug had been stopped.

By means of renal function tests run before and at the end of the coadministration of penicillin and caronamide it was ascertained that the latter compound did not influence irreversibly glomerular filtration, renal plasma flow, PAH Tm, or glucose Tm.

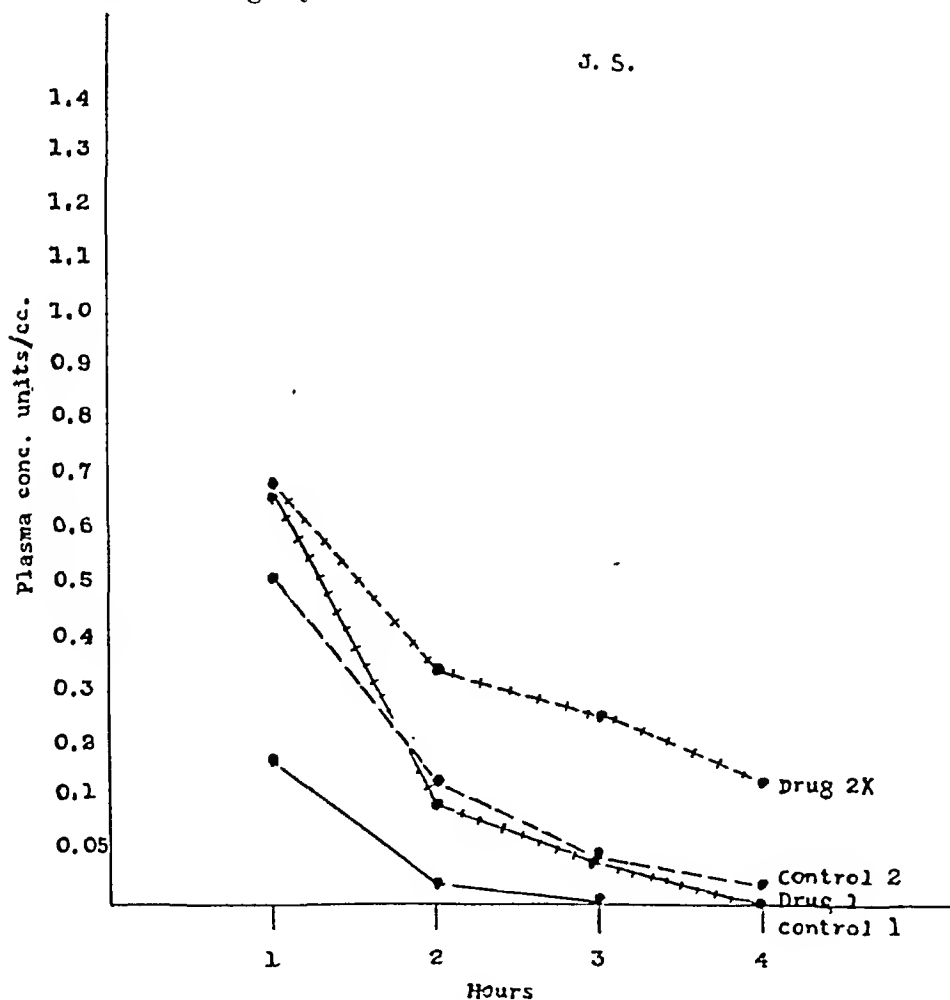


FIG. 5.—Patient J. S.: The effect of caronamide on the 4-hour antibiotic plasma level following the administration of 100,000 units of penicillin orally. C. 1 and C. 2 were two control curves wherein penicillin was administered alone. The actual dose of caronamide given orally with penicillin 1 hour before the lower drug curve was 0.5 gm. Similarly, the dose of caronamide for the top drug curve was 1 gm.

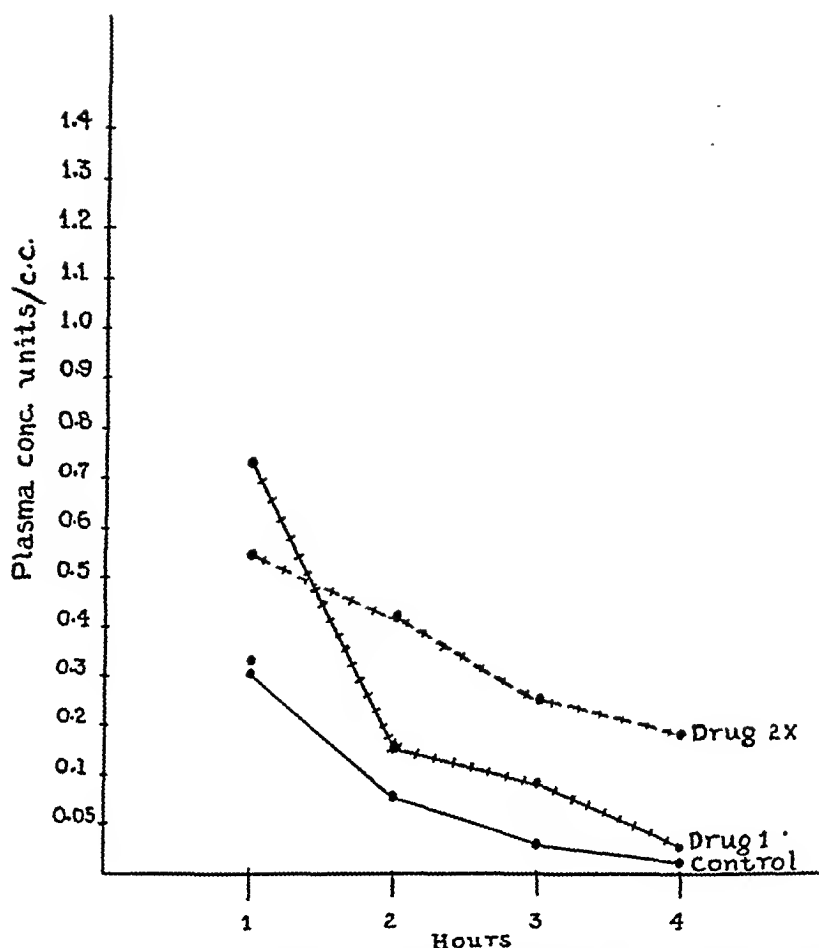


FIG. 6.—The average effect of caronamide on the 4-hour antibiotic plasma level following the administration of 100,000 units of penicillin orally. The control curve represents an average of all the corresponding values for both control phases. The coordinate for the lower drug curve are averages of all the corresponding penicillin values when the dose of caronamide administered with each dose of penicillin was one-sixth the daily dose of 0.2 gm./kg. Similarly, the caronamide dose for the top drug curve was one-sixth the daily dosage of 0.4 gm./kg.

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MYELOPHTHISIC ANEMIA THE PRESENTING MANIFESTATION OF PROSTATIC CARCINOMA WITH SKELETAL METASTASES: THE EFFECT OF CASTRATION AND STILBESTROL

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CARCINOMA of the prostate, although frequently metastatic to bone, is not often associated with severe anemia. It is the purpose of this communication to point out that myelophthisic anemia may be the presenting manifestation of prostatic cancer and that this anemia may respond to combined castration and female sex hormone administration.

Case Reports. CASE 1. J. W., a married painter of 47, was admitted to the Boston City Hospital August 17, 1929, complaining of pallor, weakness, loss of 75 pounds in weight, and pains in the arms and legs, all with onset approximately 9 months earlier. The pains had at first been intermittent but later were described as being almost continuous and extending throughout the length

of all four limbs. On occasions the pains in the arms had been shooting in character. Five months before admission he had suffered from acute urinary retention which required catheterization. There had been no other urinary symptoms prior to this nor did any develop subsequent to this single episode. Eight weeks before admission the patient awakened one morning with a left facial paralysis. He stated that on occasions he had noted edema of the legs during his illness. His past and family histories were irrelevant. He denied venereal disease.

Examination revealed an extremely pale, markedly emaciated, white man in no apparent distress, but appearing much older than the stated age. The peripheral arteries were markedly thickened. There was generalized weakness and atrophy of all the muscles of

TABLE 1.—BLOOD FINDINGS UPON ADMISSION IN 3 CASES OF MYELOPHTHISIC ANEMIA SECONDARY TO CARCINOMA OF THE PROSTATE WITH SKELETAL METASTASES

	Case 1	Case 2	Case 3
Red blood cells (millions per cmm.) . . .	2 15	2 74	2 30
Hemoglobin (gm. per 100 cc.) . . .	5 6	7 2	6 8
White blood cells (thousands per cmm.) . .	3 4	5 0	7 0
Hematocrit (%)	24 4	24 0
Mean corpuscular volume (c. micra)	89 0	104 2
Mean corpuscular hemoglobin concentration (%)	..	33 9	34 3
Reticulocytes (%) . . .	4 8	4 0	2 0
Nucleated red blood cells . . .	+	0	+
Anisocytosis . . .	+++	+	+++
Poikilocytosis . . .	+++	+++	+++
Platelets . . .	128,000	Increased	Increased
Icteric index . . .	4	3	5
Non-protein nitrogen (mg. per 100 cc.) . .	42	27	37
Differential:			
Polymorphonuclear neutrophils (%) . . .	54	67	70*
Eosinophils (%)	2	4
Basophils (%) . . .	1	1	..
Lymphocytes (%) . . .	38	11	18
Monocytes (%) . . .	7	19	8

* Bands 29.

the trunk and limbs, and pressure over muscles revealed moderate tenderness. Neurologic examination was essentially negative except for a peripheral type of left facial palsy. Heart, lungs, abdomen and skeleton were normal on physical examination. The prostate was of normal size, firm and smooth. Laboratory examinations showed the specific gravity of the urine to range from 1.005 to 1.010 with albumin and white cells constantly present. The blood non-protein nitrogen was

42 mg. per 100 cc. No free hydrochloric acid was present in the gastric juice after the subcutaneous injection of histamine. Lumbar puncture was negative. Stools were negative for occult blood. Roentgen ray examination of the skeleton revealed widespread metastatic involvement of an osteoplastic type, such as commonly originates in the prostate. Although most marked in the trunk, hip and shoulder girdles, and proximal portions of all four extremities, lesions could be seen extend-



FIG. 1.—(Case 1.) Roentgen ray of pelvis.



FIG. 2.—(Case 1.) Roentgen ray of feet.

ing to the distal tips of the fingers and toes (Figs. 1 and 2). The results of blood examination are shown in the table.

Transfusion of 500 cc. of whole blood was performed and a trial course of iron therapy was begun, which was not followed by any change in blood values. Two hundred grams of whole liver daily followed by 30 gm. of liver extract (Lilly 343) daily was unassociated with any response. A second transfusion of whole blood was given 3 weeks after admission. On October 1 gross hematuria occurred for 12 hours and then disappeared. Following this episode the patient had some difficulty in commencing urination and occasionally was incontinent. At this time repeated examination of the prostate showed it to be fixed and very firm although entirely smooth. The patient's anemia became increasingly severe and in November the prostate felt stony hard and nodular. On November 19, approximately 1 year after the onset of symptoms, the patient died. Postmortem examination was limited to the prostate which although stony hard appeared grossly normal. Microscopic examination revealed scirrhous carcinoma.

CASE 2. H. S., a married caretaker, 64 years of age, was admitted to the Boston City Hospital, December 1, 1933, complaining of increasing weakness, pallor, and loss of weight, with onset 6 months previously. For a few weeks there had been some aching in the shoulders, and in the muscles of the legs. For 3 weeks he had received iron and liver extract treatment with no noticeable effect upon his condition. There had been no urinary symptoms of any kind. His family and past histories were irrelevant. Venereal disease was denied.

Examination revealed a thin, pale, white man lying comfortably in bed. All but 3 teeth were absent. These were carious and surrounded by pyorrhea. There was moderate tenderness of the calf and shoulder muscles on pressure and atrophy and lack of tone of the calf muscles. Neurologic examination was negative. The remainder of the physical examination was normal. Rectal examination revealed a small, smooth, fixed, stony hard prostate. The urine was straw, alkaline, specific gravity 1.014, albumin negative, sugar negative, microscopic negative. Examination of the blood is shown in the table. Roentgen rays of the chest and

shoulders were negative. Roentgen rays of the pelvis and spine showed extensive osteoplastic metastases involving the entire pelvis and the lumbosacral spine. The patient was discharged to the care of his private physician. He died at home several months later.

CASE 3. H. G., a single retired barber, 78 years of age, was admitted to Cushing Veterans Administration Hospital on November 30, 1946, complaining of increasing weakness, fatigability and exertional dyspnea of 1 year's duration. Three months before admission he developed constant pain in the left axillary line at the level of the 7th rib. For several months he had nocturia and slight difficulty in starting his urinary stream, with dribbling. His family history was negative. His past history revealed recurrent malaria for several years subsequent to his initial infection in Cuba in 1898. "Creaking" of both shoulder joints on motion had been present for 20 years and occasional transitory chest and low back pain for 7 years.

Examination revealed a pale, thin, edentulous, white man in no apparent distress. The anterior-posterior chest diameter was moderately increased. The percussion note was hyperresonant. Expiratory breath sounds were prolonged. A non-tender, smooth liver edge was felt 3 cm. below the costal margin. The upper border of liver dullness was in the 8th interspace by percussion. Skeletal examination was negative except for crepitus upon movement of the shoulder joints. The prostate was enlarged, fixed, hard and contained several stony nodules. Laboratory examinations showed the urine specific gravity to vary from 1.008 to 1.020. Albumin and sugar were absent. Rare white blood cells and occasional red blood cells, hyaline and granular casts were present. Stools were negative for occult blood. Kahn test negative. The blood non-protein nitrogen was 37 mg., serum calcium 9.12 mg., phosphorus 4.3 mg., total plasma proteins 6.3 gm., albumin 3.3 gm., and globulin 3 gm. per 100 cc. Alkaline phosphatase—16.8 Bodansky units. Roentgenograms of the entire skeleton showed widespread osteoplastic metastases throughout the pelvis, upper ends of the femora, thoracic and lumbar spine and ribs.

Ferrous sulfate 0.33 gm. 3 times daily by

mouth and 15 units of concentrated liver extract daily by intramuscular injection were administered for 3 weeks. No rise in reticulocytes occurred and there was a decline in red blood cells to 2,000,000 per cu. mm. and in hemoglobin to 6.2 gm. per 100 cc. During the 4th week the patient was castrated and 5 mg. of diethylstilbestrol was given by mouth daily. Blood studies immediately after operation showed the red blood cells to be 1,990,000 per cu. mm. and the hemoglobin 5.1 gm. per 100 cc. The hematocrit was 21%. Reticulocytes were followed for several weeks. No increase occurred. A gradual rise took place in red blood cells, hemoglobin and hematocrit to values of 3,500,000 per cu. mm., 11 gm. per 100 cc. and 34% 2 months after castration. Concurrently, nucleated red blood cells disappeared from the peripheral blood and the number of band form polymorphonuclear leukocytes decreased to less than 5%. The patient's strength and sense of well-being improved markedly. Bone pains disappeared. This clinical improvement was maintained. The blood levels on July 18, 1947, 7 months after castration, were: Red blood cells, 4,000,000 per cu. mm., hemoglobin 12 gm. per 100 cc., white blood cells 6500 per cu. mm., hematocrit 36%, mean corpuscular volume 90 cu. micra; polymorphonuclear neutrophils 74% (band forms 1%), lymphocytes 25%, monocytes 1%. The red blood cells appeared normal on stained films; there was no polychromatophilia and no nucleated erythrocytes were present. Moderate regressive changes were noted in the roentgenologic appearance of the skeletal metastases. The blood values continued to remain at the same level during the next 6 months. The last observation was made Jan. 24, 1948. The patient continues asymptomatic 13 months after the institution of therapy.

Discussion. The above cases illustrate the fact that severe myelophthisic anemia accompanied by weakness and loss of weight may be the presenting manifestations of carcinoma of the prostate with extensive skeletal metastases. Examination of the prostate in Case 1 revealed little in the way of abnormality at the time of admission. Later in this case, and in the second case on admission hard-

ness and fixation of the prostate were found. However, without the Roentgen ray evidence of skeletal involvement the diagnosis of carcinoma of the prostate would have been more difficult to establish.

In Case 1 the existence of metastatic lesions extending to the distal phalanges of the hands and feet is rather remarkable since metastatic lesions rarely are found below the knee or elbow. The mechanism of myelophthisic anemia remains somewhat obscure although it would appear reasonable to believe that the hematopoietic marrow has been crowded out by the abnormal tissue. Vaughan¹⁴ believes that certain cancers deprive the hematopoietic cells of necessary nutritional factors, thus leading to an imperfect formation of blood cells.

Several recent reports have noted improvement in anemia coincidental with the modern treatment of prostatic carcinoma but no blood values have been reported.^{6,7}

A question which naturally arises is whether the effect of castration and estrogens in the last case was directly upon blood formation or indirectly through an effect on the cancerous metastases. The absence of testicular function, as in eunuchs, tends to lead to slight anemia. In 7 out of 8 such cases given methyl testosterone or testosterone propionate or both, the red blood cells and hemoglobin increase.¹⁰ Castration of rats leads to a moderate decline in red blood cell and hemoglobin values,⁴ and regeneration of blood after induced hemorrhage in such animals is less rapid than in normal rats.⁵ The administration of androgens to castrated rats leads to marrow hyperplasia and red blood cell increases,⁴ and similarly speeds the regeneration of red cells following induced hemorrhage in both normal and castrated rats.⁵ Androgen administration in rats prevents the pancytopenia which follows hypophysectomy.⁴ There is thus little evidence which would suggest that castration with the concomitant decline in androgen production would directly

lead to an increase in red blood cell formation; rather the reverse might be anticipated.

In therapeutic doses in women there is no evidence that stilbestrol produces any change in the blood.^{8,9,15} In rats no change in the bone marrow or the peripheral blood occurs with doses comparable to those used in man.¹² With excessive doses, ranging from 5 to 500 times the usual maximum therapeutic dose, rats develop anemia, leukopenia, thrombocytopenia and bone marrow hyperplasia followed by hypoplasia.^{9,11,12} In dogs massive doses first produce leukocytosis which is rapidly followed by leukopenia (eventually culminating in agranulocytosis), anemia, thrombocytopenia and bone marrow hypoplasia.^{1,2,3,9,13} The administration of 10 mg. of diethylstilbestrol to adult rhesus monkeys has been reported as having no effect on the blood except for slight anemia,³ but following the administration of carbon tetrachloride a similar quantity leads to marked anemia.³

Similar effects to those obtained with stilbestrol have occurred following the administration of estradiol benzoate to rats⁹ and to dogs.^{2,3,13} Estradiol has likewise been shown to retard red blood cell and hemoglobin regeneration after induced hemorrhage in rats.⁵ There is thus no evidence that stilbestrol stimulates erythropoiesis, but rather that in large doses it produces pancytopenia with bone marrow hypoplasia.

Although much of the above work was performed on animals and thus may not be strictly applicable to man, the fact that

in Case 3 nucleated erythrocytes disappeared from the peripheral blood and the number of band form polymorphonuclear neutrophils decreased markedly suggests that either one or both of the therapeutic procedures directly affected the carcinoma in the bone marrow. Whether this effect is a specific one for prostatic carcinoma or whether the effect is obtained by virtue of an action of estrogens on the bone producing or destroying cells is not clear. It is felt that the results obtained warrant a trial of estrogenic therapy in cases of myelophthisic anemia due to metastases from other types of carcinoma.

Summary. Three patients with myelophthisic anemia as the presenting manifestation of carcinoma of the prostate with widespread skeletal metastases have been presented. The first two of these patients were observed before present-day methods of treating carcinoma of the prostate were evolved. Each died within a few months of diagnosis with anemia controlled only by blood transfusion. The third patient, whose blood values declined during a preliminary period of treatment with iron and liver extract, was castrated and subsequently treated with 5 mg. of diethylstilbestrol daily, following which the blood values returned nearly to normal. Symptoms referable to skeletal involvement disappeared. This improvement was still present 7 months later. Although the mechanism of this response is unclear, it is suggested that the treatment so affected the metastatic cancerous tissue invading the bone marrow that more normal hemopoiesis was able to take place.

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ANTI-HISTAMINIC, ANTIANAPHYLACTIC AND ANTIALLERGIC ACTIVITY OF N-(α -PYRIDYL)-N-(α -THENYL)-N', N'-DIMETHYL- ETHYLENEDIAMINE HYDROCHLORIDE*

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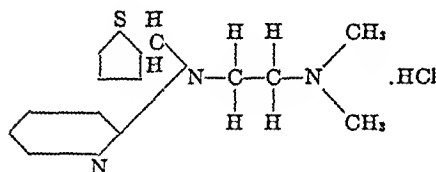
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INTEREST in the field of antihistamine therapy has stimulated a search for newer compounds possessing greater activity in allergic states than those presently available, and which at the same time may prove to be less toxic when used clinically. A promising development in this line of endeavor has been the synthesis⁶ of N-(α -pyridyl)-N-(α -thenyl)-N', N'-dimethylethylenediamine hydrochloride, supplied to us for this study under the name of Thenylene.*



This compound is closely related to Pyribenzamine and Neoantergan and differs in chemical structure by the substitution of a thiophene radical for the benzyl or methoxybenzyl ring. Thenylene, in common with other antihistaminics previously investigated, possesses marked specificity against the pharmacologic actions of histamine. It abolishes the histamine contraction of the isolated guinea pig ileum, markedly reduces the vasodepression induced by histamine in the anesthetized cat, and protects the guinea pig against the lethal effects of aerosolized or intravenous histamine. Activity against the acetylcholine and barium chloride con-

tractions of the rabbit's intestine is relatively small as compared to atropine and papaverine.⁵ Acute toxicity in mice³ is comparable to Pyribenzamine and Benadryl. Animals receiving 20 mg. per kg. of the drug for 4 weeks showed no pathologic organ changes. There have been noted in other studies, pathologic changes in the liver of some animals receiving massive doses over prolonged periods of time.⁴

In the present investigation, the antihistaminic, antianaphylactic, and anti-allergic properties of Thenylene were studied in order to make some comparison with other drugs of this series, and to gain some insight, if possible, into the relationship of antihistaminic and antianaphylactic activity to clinical efficacy in allergic states.

ANTI-HISTAMINIC ACTIVITY. A standard protective dose of 3 mg. per kg. of Thenylene was administered intraperitoneally to a group of male guinea pigs, 400 to 500 gm. in weight, 15 minutes prior to the intravenous injection of histamine (Table 1).

TABLE 1.—PROTECTIVE ACTION OF THENYLENE,
3 MG. PER KG., AGAINST INCREASING
AMOUNTS OF HISTAMINE

Histamine I.V. (mg. (base)/kg.)	No. animals	Mortality (%)
0.4 . . .	6	0
0.8 . . .	8	13
0.12 . . .	7	29
2.0 . . .	8	50
3.0 . . .	10	50
4.0 . . .	10	80
5.0 . . .	10	90
6.0 . . .	10	100

* The experimental work in this study was supported by a grant from Abbott Laboratories, North Chicago, Illinois.

* Thenylene brand of N-(α -pyridyl)-N-(α -thenyl)-N', N'-dimethylethylenediamine hydrochloride was supplied by the Abbott Research Laboratories, North Chicago, Illinois. The same drug is undergoing clinical trial by Eli Lilly & Co., under the designation of Histadyl.

The 100% lethal dose of histamine when injected into the penile vein of male guinea pigs has been determined to be 0.4 mg. per kg. of the base.¹ This standard dose of Thénylene protected all animals against 1 lethal dose of histamine, while 50% of the animals survived as much as 3 mg. per kg. of histamine, approximately 8 lethal doses. Six mg. per kg. of histamine, or 15 lethal doses, produced 100% mortality in this group of Thénylene-treated animals. The protective action of decreasing amounts of Thénylene against 1 lethal dose of histamine was also determined (see Table 2). One mg. per kg. of Thénylene

TABLE 2.—PROTECTIVE ACTION OF DECREASING AMOUNTS OF THENYLENE AGAINST 1 LETHAL DOSE (0.4 MG./KG. BASE) OF HISTAMINE

Thénylene (mg./kg.)	No. animals	Mortality (%)
1.0 . . .	10	0
0.1 . . .	10	60
0.01 . . .	10	100

prevented death in all animals tested, while 0.1 mg. per kg. protected 4 out of 10 guinea pigs against fatal shock. A dose of 0.01 mg. per kg. afforded no protection.

ANTI-ANAPHYLACTIC ACTIVITY. Male guinea pigs, 400 to 500 gm. in weight, were sensitized by the intraperitoneal injection of 0.1 cc. of normal horse serum. Twelve days later a shocking dose of 1 cc. of the same serum was administered intravenously (see Table 3). Of the controls,

TABLE 3.—PROTECTIVE ACTION OF DECREASING AMOUNTS OF THENYLENE AGAINST ANAPHYLACTIC SHOCK

Thénylene (mg./kg.)	No. animals	Mortality (%)
0 (control) . . .	14	100
1.0 . . .	10	20
0.1 . . .	14	43
0.01 . . .	10	100

100% died in typical anaphylactic shock. The remaining guinea pigs were divided into 3 groups, and given 1, 0.1 and 0.01 mg. per kg. of Thénylene respectively by intraperitoneal injection, 15 minutes prior to the shocking dose of antigen. Fatal anaphylaxis occurred in 20% of the animals receiving 1 mg. per kg. of Thénylene. A mortality of 43% occurred in the group

pretreated with 0.1 mg. per kg. Those receiving 0.01 mg. per kg. were not protected against fatal anaphylactic shock.

ANTI-ALLERGIC ACTIVITY. The clinical action of Thénylene was studied in 117 patients with 1 or more allergic complaints (see Table 4). Twenty patients had 2

TABLE 4.—CLINICAL RESULTS WITH THENYLENE

	No. treated	Im-proved	Unim-proved
Urticaria:			
Acute	5	4	1
Chronic	9	7	2
Seasonal hay fever	40	30	10
Rhinitis, perennial allergic	50	32	18
Asthma	21	7	14
Dermatitis:			
Atopic	2	1	1
Contact	5	4	1
Unclassified	2	0	2
Headache, allergic	2	0	2
Pruritis ani, allergic	1	0	1

complaints, and the effect on each was not necessarily the same. A favorable effect on certain allergic symptoms was observed, similar in nature to that exerted by other known antihistaminics. Clinical effect when present, occurred within 30 minutes following oral administration, and lasted several hours. The drug was usually administered to adults in doses of 100 mg., while one-quarter to one-half this amount was given to children. In those with constant symptoms, the drug was prescribed 4 times daily, after meals, and at bedtime. Where symptoms were intermittent it was recommended only when necessary. In many instances it was found that smaller amounts than originally prescribed were adequate in controlling symptoms.

The majority of patients with urticarial dermatoses noted a reduction of lesions and pruritus following each dose of drug. In 5 cases of acute urticaria, all but 1 experienced marked symptomatic relief, while 7 of 9 patients with chronic urticaria noted a favorable effect. Approximately 75% of acute seasonal hay fever obtained some benefit from the drug, although relief of symptoms was seldom complete. The mild discomfort occurring in some

patients who had received protective immunization against the specific allergen to which they were sensitive appeared to be more greatly benefitted than the severer symptoms of unimmunized individuals. In many cases the drug appeared to be more effective in alleviating symptoms at the onset and height of the ragweed pollinating season than in the latter days when the pollen count was declining. This has also been observed to be the case with other antihistaminic drugs. Symptomatic benefit was somewhat less in cases of non-seasonal allergic rhinitis, 64% of patients noting some improvement. The drug was used in 21 cases of asthma with benefit occurring in 7 patients. Relief of symptoms in the latter was not striking, and usually not as great as that obtained from older remedies such as epinephrine, ephedrine or aminophylline. The pruritus of atopic and contact dermatitis was notably diminished in 5 of 7 patients. In 2 other cases where the type of dermatitis could not be accurately classified, but which were felt to be allergic in nature, no help was evident. Results were negative in 2 instances of allergic headache, and in 1 case of pruritus ani.

SIDE ACTION. One or more side effects, usually mild in nature, were encountered in approximately 25% of the patients receiving the drug. These occurred most often when doses of 100 mg. were administered but rarely affected the continued administration of the drug. A reduction in dosage to 50 mg. obviated the side action in most instances. Drowsiness, which is the most common side effect noted with other antihistaminics, occurred in 13 patients. Vertigo, headache, gastro-intestinal distress and excessive dryness of mucous membranes were next in order of frequency. No serious toxic action was observed in any patients in this group. Few received the drug continuously for periods of more than 2 weeks. In 1 patient who received 400 mg. daily for 10 weeks, and in 2 others who received the same dosage for 8 weeks, no changes

in the peripheral blood or urine were observed. In view of the liver changes occurring in laboratory animals receiving large doses over prolonged periods¹, it would seem advisable to follow closely with laboratory studies any patient receiving large amounts of the drug for a long period of time.

Discussion. Thenylene compares favorably with other antihistaminic agents already in use in this country and abroad. Its activity against histamine is somewhat less than that of Pyribenzamine or Neoantergan when compared on the basis of protection afforded the guinea pig against multiple lethal doses of histamine.² When its effectiveness is measured against 1 lethal dose of histamine, or by its ability to prevent fatal anaphylaxis, it is closely comparable to other active drugs of this series. While one is tempted to make clinical comparisons between symptomatic drugs in allergy, this must be done with due regard to the variability of the allergic state in the same individual at different times. Thenylene, in the dosage employed in this study, exerts a palliative action in many allergic conditions of a similar order shown by other antihistaminics currently available. As more drugs of this group are synthesized, it becomes evident that patients who fail to obtain a favorable action from 1 compound, may react more satisfactorily to a related compound. The relatively low incidence of side action at effective dosage entitles Thenylene to a place in the growing list of palliative agents in allergy. These drugs, of course, do not replace etiologic investigation, the elimination of offending allergens, or desensitization where indicated, but act as helpful adjuncts in the control of the allergic state.

Summary. 1. N - (a - pyridyl) - N - (a - thenyl) - N', N' - dimethylethylenediamine hydrochloride (Thenylene) was investigated with reference to its effectiveness in preventing fatal histamine shock and anaphylaxis in guinea pigs, and in alleviating allergic symptoms in man.

2. As many as 15 lethal doses of histamine were required to kill some animals protected with 3 mg. per kg. of Thenylene. One mg. per kg. of the drug protected all animals against 1 lethal dose of histamine, while 0.1 mg. per kg. protected 40% against this fatal dose. Marked protection against fatal anaphylaxis in guinea pigs was observed with as little as 0.1 mg. per kg. of Thenylene.

3. Symptomatic relief for several hours

following each dose of the drug was evident in many cases of urticaria, hay fever and perennial allergic rhinitis. Results in asthma were not striking. The pruritus of allergic dermatoses were alleviated in some instances.

4. Mild side effects, such as drowsiness, vertigo and gastro-intestinal upset, occurred in 25% of those receiving the drug. These were rarely severe enough to warrant discontinuation of the drug.

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PERFORATION OF THE INFARCTED INTERVENTRICULAR SEPTUM

REPORT OF TWO CASES, ONE DIAGNOSED ANTEMORTEM

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PERFORATION of the interventricular septum as a complication of cardiac infarction is a syndrome occasionally found at autopsy and rarely diagnosed before death. The purpose of this article is to review the literature on this subject and to add 2 more cases to those previously reported. One of the present cases is the fifteenth reported case in which the diagnosis was made antemortem.

In 1934 Sager¹³ reviewed the literature with regard to perforation of the infarcted interventricular septum and reported a case of his own. At that time, including Sager's case, a total of 18 cases had been reported. Until then only 1 case had been diagnosed antemortem, Sager's case being the second. In 1943, Weber¹⁵ again reviewed the literature of this subject and reported a case of his own. Sixteen additional cases of this entity were found, of which 5 were diagnosed antemortem. Since Weber's review, 7 additional cases had been reported through July 1946 in addition to 13 cases found by Edmondson and Hoxie.⁵ Seven of these 20 cases were diagnosed antemortem. Thus, a total of 54 cases of this condition had been reported through July 1946, of which 14 were diagnosed antemortem. Weber's¹⁵ patient was a 46 year old man, who was seen 9 days after the onset of precordial pain with a rough systolic murmur over the entire precordium, maximal in the fourth and fifth left intercostal spaces and a palpable thrill in the latter area. He died 20 days after the onset of pain. Lober and Hertzog⁹ reported the case of a 65

year old white woman who developed precordial pain 7 days prior to examination. When first observed she had a systolic thrill and murmur in third and fourth interspaces to the left of the sternum. She died the day of admission. Master and Russell¹¹ report a 47 year old man who had a typical history for myocardial infarction and ECG changes of an anterior myocardial infarction. On the 3rd day of his illness, he developed a systolic thrill and systolic murmur in the fourth left interspace. Right axis deviation developed on ECG and Q3 appeared. The patient died on the 11th day of his illness. At autopsy there was acute infarction at the apex of the left ventricle as well as 2 perforations of the interventricular septum.

Wood and Livezey¹⁷ report an unusual case who survived 4 years and 10 months after his acute episode of septal perforation. The patient was a 44 year old white man seen 1 month and 6 days after coronary pain appeared. He had a loud rough systolic murmur and systolic thrill over the lower sternum. Two weeks later he developed right heart failure and 6 weeks later dependent edema which never left him. He was benefited by mercurials but very little by digitalis. At necropsy the right coronary artery was thrombosed and there was a 1.5 cm. perforation in the interventricular septum. Edmondson and Hoxie,⁵ in a review of 25,000 consecutive necropsies performed at the Los Angeles County Hospital over a 17 year period, found 865 unhealed infarcts, 72 of which

had ruptured, and 13 of which had ruptured interventricular septa. Three of these were diagnosed antemortem. The time of survival was known in 11 cases; the average of 10 was 2.25 days, the other surviving several months. In 11 of the 13 a systolic murmur was observed. Benson, Hunter and Manlove,³ reviewing 7000 autopsies, found 40 cases of cardiac rupture, 2 of which had perforated septa. One of these 2 was a 60 year old man found dead in bed; he had not been previously examined. The second was an 81 year old man who became dyspneic 8 days prior to admission. On admission he had a loud apical systolic murmur transmitted to the axilla and back. He died on the 2nd hospital day. Wood¹⁶ reported a case in a 69 year old white woman who had a severe attack of precordial pain 10 days before admission. There was on admission a blowing systolic murmur over the lower sternum, transmitted to the axilla and up the sternum. There was no thrill. ECG showed evidence of recent posterior infarction. The patient expired 5 weeks after admission.

Foster⁶ reports the case of a 67 year old white man who was hospitalized soon after the onset of substernal pain with radiation down the left arm. Physical findings are not given in his report. At autopsy, 3 days later, there was found an anterior myoeardial infarct with septal involvement and a septal perforation 1 cm. in diameter located anteriorly near the cardiac apex.

Bean² in his review of 300 cases of cardiac infarction collected from the records of the Boston City Hospital found 1 instance of infarcted septum with fresh perforation. Through the courtesy of this author we are able to report this case in more detail than appeared in his original article.

Case Reports. CASE 1. A 35 year old white American woman was admitted to the Boston City Hospital on Jan. 17, 1936. Her past history was negative except for known diabetes. The history was sugges-

tive of anginal pain first occurring 7 days before hospital admission.

P. E. P. 100; R. 30; B.P. 0/0. Obese white woman in coma and shock on admission. Heart percussed normal in size. Heart sounds were clear. There were no murmurs. Kussmaul breaking was noted. The lungs were clear to percussion and auscultation.

Laboratory Data. WBC 7000. Urine showed albumin, sugar, casts. Blood sugar 480 mg. per 100 cc. NPN 80 mg. per 100 cc.

Course. Patient was given insulin, fluids but no digitalis. She expired during the 1st hospital day.

Necropsy Findings. The heart weighed 320 gm. with body weight of 70 kg. There was marked sclerosis of the left coronary artery. The heart valves were normal. There was a fresh thrombus in the left anterior descending coronary artery occluding this vessel. The anterior portion of the interventricular septum and adjacent portions of the right and left ventricular walls were infarcted. In the anterior portion of the septum near the apex was a ragged, irregular perforation 1.5 cm. in diameter. The lungs showed moderate congestion and edema. Liver, kidneys and spleen were not remarkable. There was generalized arteriosclerosis, no evidence of emboli or other thrombi.

CASE 2. L. H., a 76 year old white woman, was admitted to the medical service of the Cincinnati General Hospital on July 10, 1947. Two weeks prior to admission the patient developed a productive cough with some substernal chest pain on coughing. She also complained of pain in the abdomen, back, left hip and left leg. For a week prior to admission she had been febrile, had had chilly sensations, and had been confined to bed. During this week she had been semi-conscious most of the time with occasional lucid intervals; also during this period she vomited frequently, and her breathing was observed to be labored. She became completely unresponsive on the day of admission.

P. E. T. 101; P. 64; R. 48; B.P. 120/80. The patient was a moderately obese, dyspneic, slightly cyanotic white female. She was not orthopneic. She was disoriented but responded to commands in a confused manner. Neck: no venous distention.



Fig. 1.—Case 2. ECG (July 10, 1947) showing Q_3 and elevated ST_3 consistent with posterior left ventricular infarction. Reciprocal ST depression in leads I and CF_4 .

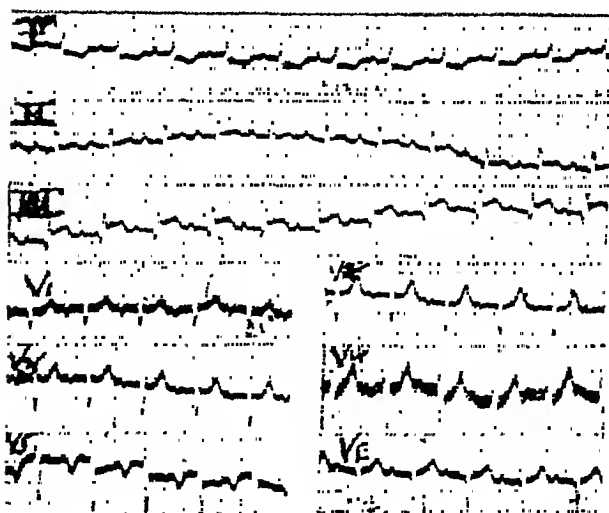


Fig. 2.—Case 2. ECG (July 18, 1947) showing Q_3 and elevated ST_3 consistent with posterior left ventricular infarction. Absent R waves in V_1 , V_2 , V_3 .

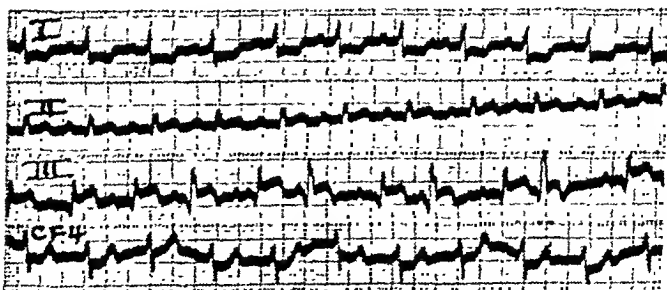


Fig. 3.—Case 2. ECG (July 23, 1947) showing interference dissociation, Q_3 and inverted T_3 , consistent with posterior left ventricular infarction.

Ocular fundi: tortuous arterioles and A-V nicking. Mouth: edentulous. Tongue dry. Chest: over the right lower lobe posteriorly there were impaired resonance, fine râles and suppressed breath sounds. Heart: point of maximal impulse in sixth left intercostal space 2 cm. from midclavicular line. Rate slow; rhythm regular. *No murmurs*. Abdomen: slight generalized tenderness and increased resistance to palpation. No masses. Liver thought to be percussed 4 cm. below right costal margin. Extremities: bilateral calf tenderness and 1+ pretibial edema, but Homan's sign negative. Two small purpuric spots were seen on the right leg. Neurologic: all deep reflexes were hyperactive. There was a questionable Babinski on the right. Pelvic and rectal: negative.

tricular rate 60. QRS 0.06 sec., QT 0.32 sec.; Q3 present. July 12, interference dissociation. Q2 and Q3 present; ST2, ST3 elevated; ST1, ST4 depressed. July 16, same. July 18, 1947. (Fig. 2.) Sinus rhythm. PR 0.22 sec. QRS 0.08 sec. QT 0.36 sec. Q3 present. ST1 depressed, ST3 elevated. Q wave in V1, V2, V3, VE. ST in V5 depressed with T inverted. July 23, 1947. (Fig. 3.) Rate 100. PR 0.20 QT 0.26. Q3 present. ST3 elevated. ST1, 4 low, sagging. Nodal premature beat.

Chest Roentgen Ray. July 10, 1947. Heart 14.5 cm. in chest of 22.5 cm. Suggestive bilateral pulmonary edema. Area of increased density in right midlung field read as possible infarct.

Course. The patient was given penicillin for the first 10 days of her hospital stay.

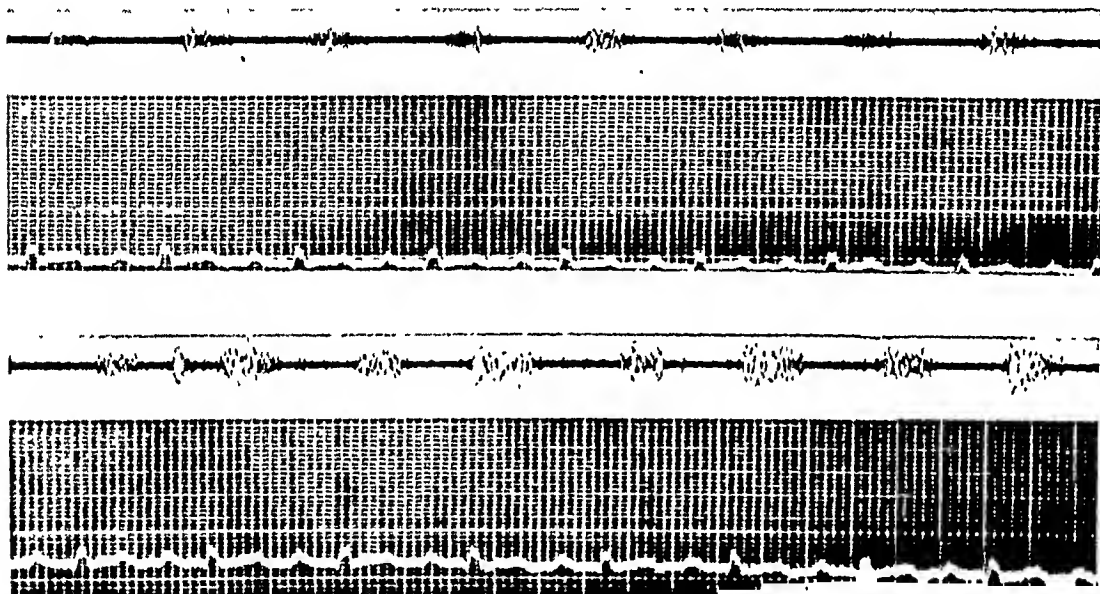


FIG. 4.—Case 2. Lower tracing taken at full volume. Upper tracing taken at approximately half volume

Laboratory Data. Hgb. 15 gm.; RBC 3,750,000; WBC 26,700 on admission; 94% polymorphonuclears and 6% lymphocytes. WBC 18,500 2 days before death. Cath. urine; sp. grav. 1025; Alb. 1+ no sugar; rare RBC, no WBC or casts. Stools guaiac negative, yellow. Kahn, neg. BUN 60 mg. % on admission, later 70, 100, and 90 on day of death. CO₂ 38 vol. % day of death. Blood culture negative. Prothrombin times 17 sec., later 24.5 and 24.2 2 sec.

ECG. July 10, 1947. (Fig. 1.) Interference dissociation. Auricular rate 100; ven-

Her temperature became normal on the 3rd day and remained so except for elevations to 100° during the 3 days prior to death. On the morning following admission the heart rhythm was found to be irregular with pauses occurring every 2 to 8 beats. The runs of 2 to 8 beats seemed to be regular. On the 7th hospital day a harsh Grade 4 (Levine) systolic murmur was audible over the entire precordium. This murmur was loudest in the fourth left intercostal space just to the left of the sternum. (Fig. 4). Phonocardiogram tracings taken on July 24

with microphone over fourth left intercostal space 3 cm. from sternum showed loud murmur filling nearly all of systole. A systolic thrill was felt in this area and at the cardiac apex. Two days prior to death the patient, who was previously only slightly improved, seemed worse. She became dyspneic with associated periods of apnea and began to run slight fever. On the 15th hospital day the patient was found to be unresponsive. B.P. 85/70. Respirations were 48. There was dullness and bronchial breathing over the right upper lobe. Lung

thrombi; (4) recent perforation of interventricular septum through a fresh infarct; (5) multiple pulmonary emboli and pulmonary infarction; (6) chronic passive congestion of viscera with cardiac cirrhosis; (7) acute thrombosis of iliac, perivesical, uterine, right ovarian, renal veins; (8) squamous metaplasia of pancreatic duct with small foci of fat necrosis; (9) fibrosis of suprarenal capsule; (10) hemopericardium.

Gross Description of Heart (Figs. 5 and 6). The heart weighed 350 gm. The pericardial sac contained 24 cc. of grossly bloody fluid.

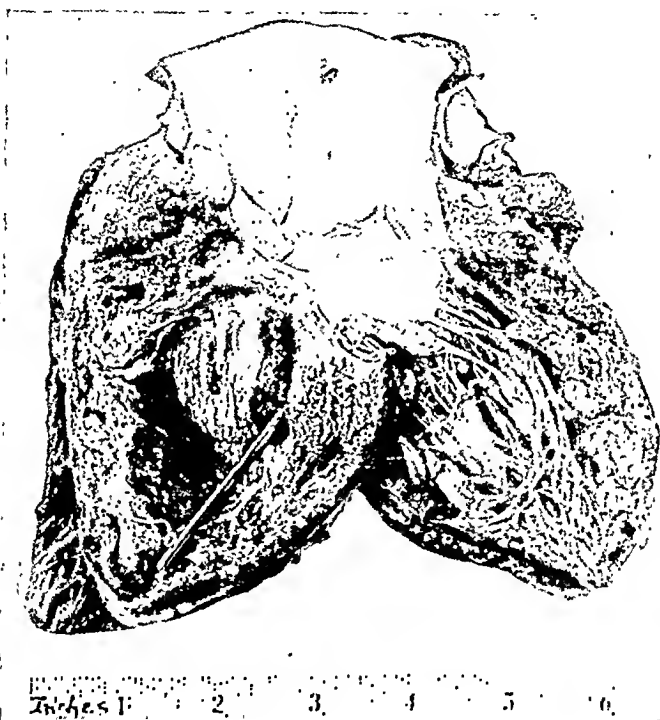


FIG. 5.—Anterior view of heart showing endocardial surface of left ventricle. Probe marks septal perforation. (Scale in inches.)

bases were clear. Left border of cardiac dullness was 11 cm. from the midsternal line. The systolic thrill and murmur were present as before. There was no cyanosis. The patient expired later the same day.

Antemortem Diagnoses. (1) Posterior myocardial infarction; (2) probable perforation of infarcted interventricular septum; (3) probable bronchopneumonia or possible pulmonary infarction.

Necropsy Diagnoses. (1) Coronary atherosclerosis; (2) extensive progressive myocardial infarction; (3) old and recent mural

The surface of the left ventricle showed petechial hemorrhages and large areas of pallor and yellowish discoloration. The epicardium was clouded in these areas and the underlying myocardium softened. Cardiac chambers were dilated with softening of the entire myocardium. The entire interventricular septum was soft, mushy, and yellow-gray as were the adjacent parts of both ventricles. There was also a section of the midportion of the left ventricular wall having the same consistency, all of these areas representing sites of old and

recent infarction. There was a large mural thrombus in the left ventricle and smaller mural thrombi in the right ventricle and right auricle. There was a complete perforation of the interventricular septum 1 cm. in diameter located 2 cm. below the mitral valve on the left side and just beneath the septal flap of the tricuspid valve on the right side. This perforation was 1.5 cm. from the epicardial surface of the left ventricle. It was ovoid in shape with irregular edges. The coronary arteries showed athero-

only 6.4 days. Six survived over 1 month but less than 1 year. One extraordinary case survived 4 years and 10 months.¹⁷ Electrocardiographic findings were unknown in 38 cases; of the remaining 16, 4 showed posterior infarction; 4 "cardiac infarction," 1 anterior infarction, 1 complete block, 5 RAD, 1 RBBB, and 2 a large Q3. The signs were unknown in 10 cases; there were none in 2 cases. Of the 45 in whom physical findings were

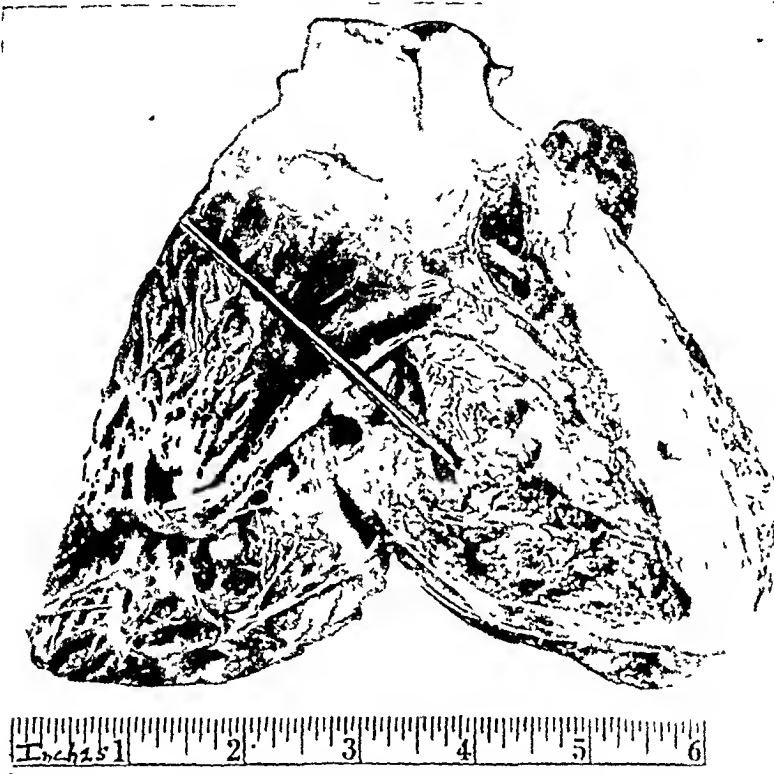


FIG. 6.—Anterior view of heart showing endocardial surface of right ventricle. Probe marks septal perforation. (Scale in inches.)

matous and calcified plaques. The left coronary was occluded at its bifurcation by an atheromatous and calcified plaque. Similar luminal stenosis occurred 15 mm. distal to this in the left anterior descending branch. The right coronary ostium was narrowed by an atheromatous plaque in the aorta, but there was no area of occlusion apparent.

Discussion. In the 56 total cases, including the present, the time of survival after septal perforation was known in 38. Of these, 31 survived less than 1 month; these 31 had an average survival time of

known, 43 showed systolic murmurs, usually maximal to the left of the lower sternum; 22 of the 45 showed systolic thrills; only 3 showed diastolic murmurs, and none showed diastolic thrills.

The 2 cases in which no murmur was heard were those of Bean,² and Bickel and Mozer.⁴ The latter of these was a man 87 years old who had been well until 15 days before hospital admission. At this time he developed rather suddenly cough, dyspnea, anorexia and weakness.

He had no chest pain at any time. On admission he had Cheyne-Stokes breathing, heart sounds of poor quality, but a blood pressure of 150/70. He had signs of bronchopneumonia. No murmur was heard, and there is no mention of any pulmonary or cardiac condition which might obstruct the transmission of a murmur. The patient died on the 5th hospital day after an uneventful clinical course. At autopsy there were found thrombi obstructing both coronary arteries and a septal infarct with perforation. This perforation was in the posterior part of the septum and measured 2×0.5 cm.

Bickel and Mozer attributed the absence of any murmur in this patient to the large size of the septal perforation. In their discussion of the case they state that they regarded the cardiac tone and blood flow as adequate for the production of a murmur provided proper local conditions were present.

Bean's case also had a large septal perforation, but here the patient was in coma and shock and the blood pressure unobtainable. Among the other cases reviewed in the present paper were several with septal perforations as large or larger than Bean's, or Bickel and Mozer's cases, and in all of these murmurs alone or murmurs and thrills were found. In addition there appeared to be no correlation between the size or location of the perforation and the intensity of the murmur.

In Sager's¹³ review, 15 of 18 cases gave a history typical of coronary occlusion. The physical findings, according to him, are those usually found in cases of patent interventricular septum. When both of these conditions occur in the same patient, the diagnosis of perforation of the infarcted septum is to be made. The murmur is usually loud, according to Sager, usually accompanied by a thrill, and transmitted to the left axilla but not to the neck vessels. He explains the infrequency of septal perforation as compared to that of rupture of the ventricular wall by the rich arterial supply to the septum.

According to Weber,¹⁵ the diagnosis of perforation of the infarcted septum is made by the sudden appearance of a loud systolic murmur and a palpable thrill in a patient who is known to have myocardial infarction. He states that the prognosis is much worse in this condition than in the usual case of myocardial infarction, not because the perforation interferes with cardiac dynamics, but because the perforation is ordinarily seen only in cases of massive infarction. He states that the left coronary artery is usually occluded in these cases, and that in addition the right coronary is usually sclerosed and incapable of aiding in anastomoses. Lober and Hertzog⁹ state that symptoms at the time of perforation are unusual, but if the patient lives long enough, there always develops an intractable right-sided heart failure, death from heart failure being inevitable. Wood and Livezey¹⁷ make the same statement.

The conditions to be differentiated from perforated septum are rupture of a papillary muscle of the left ventricle following cardiac infarction, congenital potency of the interventricular septum, perforation of the septum due to subacute bacterial endocarditis, and rupture of a mitral chorda tendinea.

With rupture of a papillary muscle complicating infarction, the heart, according to Sager,¹³ usually becomes markedly dilated, the murmurs are even louder, and diastolic murmurs are more common. Too, the signs are evenly distributed over the precordium, or maximal at the apex. Weber states that here there is a more sudden change for the worse, and more likelihood of left-sided than right-sided heart failure. Until July 1946, only 16 cases^{6,7,8,10,12,14} of ruptured papillary muscle following cardiac infarction are recorded with physical examination of the heart. Of these, 6 had an apical systolic murmur, 1 had an apical diastolic murmur, 3 had an apical systolic and diastolic murmur; 1 had "murmurs," 1 had "noises," 1 had a friction rub in the

fourth left interspace and an apical gallop; in 2 no murmurs were heard, and in 1 case there was no mention of murmurs. The prognosis in this condition is approximately that of the former one. Of 23 reported cases of ruptured papillary muscle which can be attributed to coronary occlusion, only 1 survived longer than 1 month. In the remaining cases the average survival was 4 days.

Congenital patency of the interventricular septum may cause confusion, but should be easily differentiated by the absence of history or ECG changes of myocardial infarction. It would presumably be impossible properly to diagnose a patient having a previously undiagnosed congenitally patent septum complicated by myocardial infarction. Acquired perforation of the septum due to subacute bacterial endocarditis is to be differentiated by the positive blood cultures and the presence of embolic phenomena. Perforation of the infarcted septum must also be differentiated from ruptured chordæ tendineæ, according to Bailey and Hickam.¹ The latter condition is to be suspected in a middle-aged or elderly individual who suddenly, without dramatic incident, develops a loud systolic murmur, usually with a thrill, maximal at the cardiac apex and along the left sternal border. Congestive heart failure does not usually ap-

pear in these cases for months or years. The absence of clinical or laboratory evidence of cardiac infarction serves to differentiate ruptured chordæ from acquired patency of the infarcted interventricular septum.

Summary. Two cases of perforation of the infarcted interventricular septum are reported in 1 of whom the diagnosis was made antemortem.

A total of 56 such cases have been found in the literature; 15 of these were diagnosed antemortem. In 38 whose survival time was known, 31 survived less than 1 month, 37 less than 1 year, and 1 survived 4 years and 10 months. Forty-three cases of 45 examined showed systolic murmurs, usually maximal to the left of the lower sternum; 22 showed systolic thrills; only 3 showed diastolic murmurs.

The diagnosis should be suspected in any patient known to have a myocardial infarction who suddenly develops a systolic murmur and thrill to the left of the lower sternum. The only condition likely to be confused is rupture of a papillary muscle following cardiac infarction, where the condition of the patient suddenly becomes worse, the murmurs are louder and nearer the apex, and the ensuing failure is left-sided rather than right-sided.

Authors' Note: Since the submission of this article for publication 2 additional cases of rupture of the interventricular septum as a complication of myocardial infarction have been reported. One case was reported by D. CARROLL and S. D. CUMMINS: *Am. Heart J.*, 34, 893, 1947. The other by R. S. DIAZ-RIVERA and A. J. MILLER: *Am. Heart J.*, 35, 126, 1948. The first case showed a loud apical systolic murmur, heard also over precordium and the left upper quadrant. The second showed an apical systolic murmur heard also in the third left intercostal space. No diastolic murmur or systolic thrill was described in either case.

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THE USE OF VITAMIN E IN HEART DISEASE

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EARLY in 1946 attention was called by Vogelsang and Shute¹¹ to the marked improvement resulting from the administration of vitamin E to patients with various forms of heart disease. Considerable publicity was given to the phenomenal therapeutic results claimed in congestive heart disease and angina pectoris by those authors. Evan Shute¹⁰ was quoted as saying: "We have not learned of a single failure. The percentage of success is remarkable." Patients began to request the treatment from physicians, and less scrupulous drug houses quoted entire paragraphs from the articles recommending vitamin E, in their attempts to sell preparations of alpha-tocopherol. Editorial comment in the *Journal of the American Medical Association*,² however, decried this publicity given to unconfirmed work, stating "nothing in the known pharmacological actions of vitamin E would lead one to expect either a vasodilating action, a myotonic effect or an ability to repair damaged heart muscle in human beings."

Because of the widely divergent views quoted above, we decided to investigate the influence of vitamin E on various cardiac conditions. Preliminary studies were begun in August, 1946, and we are reporting here our observations on the first 25 patients studied.

Plan of Study. Cases for this study were selected from the Cardiac Clinic of the Jewish Hospital and the private practice of one of us (S. B.). After a complete history, physical examination, blood count, blood Wassermann, urinalysis, electrocardiogram and

orthodiagram, a brief period of clinical observation was carried out. The patients were then given orally 400 mg. of vitamin E* daily in divided doses. Within 2 to 4 weeks this dose was reduced to 300 mg. daily. The patients were then followed for 3 to 6 months, whenever possible. Electrocardiographs were repeated at 2- to 4-week intervals. Those patients previously receiving such preparations as digitalis, mercurials, phenobarbital, and the like, were continued on their medication so that we could more accurately evaluate the effect of the vitamin E. In some cases after the vitamin E was given, either digitalis or mercurials were then discontinued, to determine if recurrence of the cardiac failure would be prevented. In some of those patients exhibiting apparent symptomatic response to vitamin E therapy, similarly appearing tablets of calcium gluconate were substituted as a placebo.

Results. Of the 25 patients treated with vitamin E, 22 were considered to have been adequately followed, and form the basis of this report. Of these, 11 had congestive heart failure and 5 angina pectoris. The remaining 6 had hypertension and/or arteriosclerotic heart disease, without failure or angina. The essential features of these 3 groups of cases are shown in Tables 1, 2 and 3 respectively. A summary of the therapeutic results obtained is presented in Table 4.

CONGESTIVE FAILURE (Table 1). Of the 11 patients with congestive heart failure, 3 are listed as questionably improved. In Case No. 2, there was diminution in the frequency of attacks of paroxysmal nocturnal dyspnea. However the patient had discontinued working in a

* Vitamin E in the form of 100-mg. tablets of Ephynal Acetate was kindly provided for this study by Hoffman-La Roche Company.

TABLE 1.—DATA IN 11 PATIENTS WITH CONGESTIVE FAILURE TREATED WITH VITAMIN E

Case	Age	Sex	Severity	Failure		Clinical diagnosis	Electrocardiogram	Orthodiagram	Daily dose of vitamin E	Results
				Clinical features	Exertional dyspnea					
1	32	F	Mild			Rheum. h.d.; aort. st. and reg.; mitr. st. and reg.	Auric. extrasystoles; auric. dis.	Normal size; contour of mitral stenosis	400 mg. 3 wks. 300 mg. 22 wks.	After vitamin E given for 2 mos. dyspnea increased, necessitating digitalization; subsequent relief
2	60	F	Mod.			Hypert. h.d.	Myocard dis.; dig. effects	Normal size; shape suggests left ventricular hypertrophy; tortuous aorta	400 mg. 5 wks. 300 mg. 11 wks.	Moderate symptomatic improvement but patient stopped working in factory during course of study
3	54	F	Mod.			Rheum. h.d.; mitr. st. and reg.	Auric. fib.; myocard. dis.; dig. effects	30% enlargement; dilated pulm. art.; enlarged l. auric.	400 mg. 6 wks. 300 mg. 19 wks.	Increase of failure after being on vitamin E for 6 mos.; mercurial diuretics necessary
7	65	F	Mild			Hypert. h.d.	Normal	20% enlargement; tortuous aorta	400 mg. 9 wks. 300 mg. 14 wks.	Decrease in dyspnea when on vitamin E; effect duplicated by placebo
10	67	M	Marked			Hypert. and a-s. h.d.	Auric. fib.; ventric. extrasyst.; intra-vent. cond. defect; l. vent. hypert.	70% enlargement	400 mg. 19 wks. 300 mg. 4 wks.	Marked subjective improvement shortly after starting vitamin E; rapid progress of failure when digitalis was stopped, while vitamin E was continued; re-control of failure by digitalis; further subjective improvement with placebo
11	44	M	Mild			Rheum. h.d.; mitr. st. and reg.	Auric. fib.; dig. effects	40% enlargement; dil. pulm. art.; dil. l. auric.	400 mg. 8 wks. 300 mg. 5 wks.	No effect noted; stopped attending clinic after 13 wks.
15	71	M	Marked			Hypert. and a-s. h.d.	Auric. fib.; complete heart block; myocard. dis.; dig. effects	74% enlargement	400 mg. 2 wks. 300 mg. 4 wks.	Congestive failure progressed after taking vitamin E for 6 wks. (along with digitalis and mercurials); hospitalization necessary; response to bed rest, digitalis, diuretics
18	47	F	Marked			Rheum. h.d.; mitr. st. and reg.; tricuspid reg.	Large P waves; dig. effects	Marked enlargement*	400 mg. 3 wks.	Mercurials stopped after vitamin E given for 2 wks.; failure became more marked
20	62	F	Marked			Hypert. and a-s. h.d.	Left bundle branch block; myocard. dis.	68% enlargement	400 mg. 5 wks. 300 mg. 8 wks.	Felt better while taking vitamin E and mercurials were discontinued; however, at this time she was in bed because of acute thrombophlebitis; on resuming activity failure progressed, necessitating further use of mercurials, despite continuation of vitamin E
21	18	M	Marked			Rheum. h.d.; mitr. st. and reg.; tricuspid reg.	Rt. axis dev.; auric. fib.; myocard. dis.; dig. effects	Marked enlargement*	400 mg. 2 wks. 300 mg. 3 wks.	Mercurials stopped when vitamin E begun; failure gradually became more marked
22	43	F	Marked			Hypert. h.d.	Normal	Mod. enlargement*	400 mg. 10 days	No improvement with vitamin E in addition to digitalis and mercurials; later response to digitalis and mercurials alone

* Teleroentgenogram; patients unable to stand for orthodiagram.

BAER, HEINE, GELFOND: VITAMIN E IN HEART DISEASE

TREATED WITH VITAMIN E

Case	Age	Sex	Severity of angina	TABLE 2.—DATA IN 5 PATIENTS WITH ANGINA PECTORIS TREATED WITH VITAMIN E			Results
				Clinical diagnosis	Electrocardiogram	Daily dose of vitamin E	
9	77	F	Mod.	Hypert. h.d.	L. ventric. hypert., old post. infarction	Orthodiagram 30% enlargement 400 mg. 3 wks. 300 mg. 4 wks.	No improvement No improvement; left bundle branch block, present just before vitamin E started, disappeared for several months but reappeared transiently while vitamin E was still being taken
13	62	F	Mod.	Hypert. h.d.	Previously: left ventric. hypert.; intraventric. conduction defect; prob. antero-septal branch block just prior to study; left bundle branch block	400 mg. 7 wks. 300 mg. 17 wks.	Questionable slight decrease in frequency of attack
11	69	M	Mod.	A-s. h.d.	Normal	400 mg. 2 wks. 300 mg. 4 wks.	Questionable slight decrease in frequency of attack
17	73	M	Mod.	Hypert. h.d.	L. ventric. hypert.	Normal 57% enlargement 400 mg. 3 wks. 300 mg. 12 wks.	Slight improvement in exercise tolerance, which occurred however coincidentally with milder weather; no change when vitamin E discontinued
19	11	M	Mod.	Mycard. dis.	Normal	400 mg. 3 wks.	Three weeks after beginning vitamin E angina increased and myocardial infarction developed; confirmed by electrocardiographic changes

TREATED WITH VITAMIN E

DISEASE TREATED WITH VITAMIN E

Case	Age	Sex	Clinical features	TABLE 3.—DATA IN 6 PATIENTS WITH HYPERTENSION AND/OR ARTERIOSCLEROTIC HEART DISEASE TREATED WITH VITAMIN E			Result
				Clinical diagnosis	Electrocardiogram	Daily dose	
4	28	M	Nervousness; h.p. 180/120	Essential hypertension	Normal	400 mg. 5 wks. 300 mg. 25 wks.	No effect noted
5	73	M	Mycard. infarction in 1911; slight dizziness on effort	Hypert. and A-s. h.d.	Mycard. dis. intraventric. conduction defect; healed ant. and post. infarctions	400 mg. 4 wks. 200 mg. 11 wks.	No effect noted
6	17	M	Mycard. infarction in Feb. 1916; vague anterior chest discomfort	A-s. h.d.	Healed antero-lateral infarction	400 mc. 4 wks. 300 mc. 22 wks.	No effect noted
8	38	F	Disseminated; hot flushes; h.p. 220/120	Hypert. h.d.	L. ventric. hypert.; myocard. dis.	400 mg. 1 wk. 200 mg. 2 wks. 300 mg. 10 wks.	Subjective improvement (headaches); effect duplicated by placebo; h.p. unchanged.
12	53	F	Headaches; h.p. 200/120	Hypert. h.d.	L. ventric. hypert.; myocard. dis.	100 mc. 4 wks. 300 mc. 17 wks.	No effect noted
16	72	M	Dyspnea on effort; h.p. 210/100	A-s. and hypert. h.d.	L. ventric. hypert.; myocard. dis.	100 mc. 4 wks. 300 mg. 2 wks.	No effect noted

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factory at about the time of her symptomatic improvement, so that it was difficult to determine whether the medication or the decreased activity was responsible. Case No. 7 displayed a decrease in dyspnea, but this effect was also produced by the administration of a placebo. Case No. 10 claimed marked lessening of his dyspnea and precordial discomfort within a week after beginning vitamin E. However, when digitalis was stopped while vitamin E was continued, signs of cardiac failure appeared (increased dyspnea, tachycardia, pulmonary congestion). Compensation was restored with digitalis, and when a placebo was administered, the patient again claimed marked improvement.

failure, developed such an episode after he had been taking vitamin E for 6 weeks. Hospitalization and complete bed rest became necessary.

In none of the 11 patients with congestive heart failure was a definite therapeutic effect of the vitamin E noted.

ANGINA PECTORIS (Table 2). Of the 5 patients with angina pectoris, 2 are listed as questionably improved. In Case No. 14 there was possibly a slight decrease in the frequency of anginal seizures. Patient No. 17 claimed slight improvement in exercise tolerance. This occurred, however, coincidentally with the arrival of milder weather. There was no increase in symptoms when the vitamin E was discontinued. Two patients (Nos. 9 and 14)

TABLE 4.—RESULTS OF TREATMENT OF 22 PATIENTS WITH HEART DISEASE WITH VITAMIN E

	Cardiac	Angina	Hypertension and/or arteriosclerotic heart disease	Totals
Markedly improved	0	0	0	0
Definitely improved	0	0	0	0
Questionably improved . . .	3	2	1	6
Unimproved	5	2	5	12
Worse	3	1	0	4
	<hr/> 11	<hr/> 5	<hr/> 6	<hr/> 22

The remaining 8 cases were either unimproved or became distinctly worse during therapy with vitamin E. In 3 cases (Nos. 18, 20, 21), mercurial diuretics, which previously had been administered regularly, were discontinued during our treatment with vitamin E, in order better to evaluate the effectiveness of the therapy. In all these instances the cardiac failure progressed and the mercurials again had to be given. Three of these 8 patients became distinctly worse while taking vitamin E. Patient No. 1 developed increasing dyspnea and did not obtain relief until digitalis therapy was instituted. In Case No. 3, edema and dyspnea increased after the patient had been on continuous vitamin E therapy for 6 months; mercurial diuretics were then effectively employed. Patient No. 15, who had previously suffered several bouts of severe congestive

showed no improvement and 1 (No. 19) became distinctly worse. He developed an acute myocardial infarction 3 weeks after the vitamin E was begun.

In none of these 5 patients with angina pectoris was there unequivocal evidence of improvement during treatment with vitamin E.

HYPERTENSION AND/OR ARTERIOSCLEROTIC HEART DISEASE (Table 3). Of the 6 patients in this group, none exhibited a definite therapeutic response to vitamin E. In 1 (No. 12) there was a decrease in the incidence and severity of the headaches, but this effect was duplicated by a placebo.

EFFECT ON BLOOD PRESSURE, ELECTROCARDIOGRAM AND ORTHODIAGRAM. There was no definite alteration in the blood pressure of any of the patients. Serial electrocardiograms revealed no significant changes in any case. Case No. 13 illus-

trates the transitory nature of certain changes unrelated to therapy. A left bundle branch block present just prior to the beginning of this study, disappeared for several months during the administration of vitamin E. It reappeared, however, and again disappeared while the drug was still being taken. There were no changes in the orthodiagrams, except for the slight increase in heart size of several patients while their failure was becoming more severe.

Discussion. A study such as this is open to a number of criticisms. The series of cases presented is small. Furthermore, in evaluating the effect of a drug in congestive heart failure or angina pectoris, it would have been preferable to present data obtained more objectively, such as circulation times, exercise tolerance tests, venous pressure, and vital capacity. We had indeed intended expanding our studies to include these observations, but the discouraging results presented in this preliminary report deterred us from carrying these investigations further.

A consideration of the literature reveals little basis for recommending the use of vitamin E in human heart disease. The early experimental observations included the effects of vitamin E deficient diets on a cow,⁶ rabbits,⁶ chicks¹ and rats,⁷ and on isolated heart muscle strips.⁴ These results have not been uniform. For example, one observer⁷ reported cardiac disturbances in rats fed vitamin E deficient diets. Another,³ however, found no striking change in the cardiograms of rats fed vitamin E deficient diets for 1 year.

Even if we accept the debatable conclusion that vitamin E deficient diets in animals produce cardiac abnormalities, it does not appear logical to assume that vitamin E would therefore be of value in the treatment of such varied cardiac disturbances in human beings as rheumatic heart disease, angina pectoris and congestive failure. At no time has there been any demonstrable proof that patients with cardiac failure or angina pectoris are defi-

cient in vitamin E. It would appear just as illogical to recommend thiamin chloride or calcium salts or thyroid for all patients with heart disease, because prolonged deprivation of these agents may be associated with clinical or electrocardiographic changes.

The only publications to date attesting to the beneficial effects of vitamin E in humans have been those of Vogelsang, Shute and Shute.^{8,9,12,13,14} Certainly if one reviews their articles critically, one hesitates to recommend vitamin E with the degree of enthusiasm they have manifested. As a matter of fact, some of the data they present hardly warrant the conclusions reached. In one of their papers,¹² for example, they present summaries of 10 cases treated with vitamin E. In Case No. 2, they state: "she insisted on stopping the dose of ephynal on March 29, and reverted to her digitalis instead. Her relief was immediate." In Case No. 3, the regression of electrocardiographic changes in a patient with acute rheumatic fever are attributed to vitamin E therapy, rather than the natural course of the disease. In Case No. 6, the description of the cardiograms suggests acute myocardial infarction. Decrease of the chest pain need not have been due to vitamin E. Many patients with acute myocardial infarction have less pain on the 2nd day than the first. In Case No. 8, the improvement was attributed to vitamin E after a month of vitamin E therapy, even though digitalis was begun 2 weeks before improvement was noted.

In their most recent paper Vogelsang, Shute and Shute¹⁴ present a summary of their findings in 126 unselected cases of heart disease, and discuss some of the underlying pathologic physiology. They stated that improvement following therapy with vitamin E occurred because vitamin E (*a*) affects the blood-vessels, (*b*) affects the myocardium, (*c*) may influence the pacemaker of the heart, and (*d*) may influence the thrombotic features of coronary artery disease by improving the col-

lateral circulation in the ischemic area. We are not familiar with any proof of these mechanisms in the experimental animal or in man. They concluded that the great majority of cases with angina, rheumatic heart disease, congestive failure and hypertension are helped considerably by the administration of vitamin E.

Our results are so at variance with those published that we hesitate to recommend the use of vitamin E in cardiac disease. Certainly much more scientific work must be done in this field before suggestions are made that so appreciably alter our present forms of cardiac therapy.

Conclusions. 1. Vitamin E in 300 to

400 mg. doses daily was used in the treatment of 11 patients with congestive heart failure, 5 patients with angina pectoris and 6 patients with hypertension and/or arteriosclerotic heart disease.

2. In no case was there any demonstrable effect on the electrocardiogram, orthodiagram or blood pressure.

3. None of the 22 patients was markedly or moderately improved. Six patients were questionably improved and the remainder showed no change or became distinctly worse.

4. Our results were not encouraging enough to recommend the use of vitamin E in the treatment of angina pectoris, congestive failure or hypertension.

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OSTEOPOROSIS OCCURRING DURING POTASSIUM THIOCYANATE THERAPY FOR HYPERTENSIVE DISEASE

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AFTER the extensive use of potassium thiocyanate in the treatment of hypertension, occasional instances of osteoporosis and arthralgia were noted at this clinic. Since no previous description of this phenomenon could be found, a further investigation was undertaken.

The records of 5000 consecutive patients with hypertension who had been seen on two or more occasions at the Mayo Clinic in the period 1939 to 1944, inclusive, were reviewed. Potassium thiocyanate had been given to 360 patients of this group. Unexplained osteoporosis occurred in 7. Since 1944 there have been 4 additional patients with this syndrome. No history of trauma or injury at onset could be elicited from these patients. One or more extremities, usually the lower, were involved. Patients with involvement of the spine or pelvis were not included, as senile osteoporosis could not be excluded. Similarly omitted were those who had a diagnosis of chronic infectious arthritis, peri-arthritis, rheumatoid arthritis or fibrositis. Unexplained osteoporosis was not observed in the group of more than 5000 patients with hypertension who were not receiving potassium thiocyanate.

Clinical Data. A summary of pertinent clinical data is given in Table 1. The incidence of osteoporosis in the group

of patients who were receiving potassium thiocyanate therapy was approximately 2%. There were 6 women and 5 men. The age ranged from 46 to 68 years (average 56.5). The dosage of the drug varied considerably during the course of treat-

ment, but was usually in the range of 6 to 9 grains (0.4 to 0.6 gm.) daily. Onset of symptoms associated with the osteoporosis generally occurred in 3 to 6 months after administration of the drug was started. They consisted of (1) pain on use of the extremity which began insidiously and gradually increased in severity, and (2) subsequent mild swelling of the joint or joints involved, but with no acute inflammatory reaction. The severe cases simulated those of extensive posttraumatic osteoporosis. Roentgenograms, which were limited to the involved regions, revealed mild to marked diffuse osteoporosis.

Active therapeutic measures directed toward the osteoporosis were carried out in 7 cases while thiocyanate therapy was being continued. These consisted of physiotherapy, active and passive movement, shoe corrections, walking-casts, elastic bandages, and preparations of calcium and phosphate for oral use. Symptoms continued to progress despite these measures in 6 cases. Slight improvement

* Abridgment of thesis submitted by Dr. Hinchey to the faculty of the Graduate Hospital of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Orthopedic Surgery.

TABLE 1.—OSTEOPOROSIS OCCURRING DURING POTASSIUM THIOCYANATE THERAPY FOR HYPERTENSIVE DISEASE: CLINICAL DATA

Case	Age (years)	Sex	Potassium thiocyanate grains daily (average)	Blood pressure (mm. of mercury)		Onset of symptoms (months*)	Part of body involved	Condition after specific therapy	Time for improvement (months)
				Before therapy	During therapy				
1	49	F	6	159/120	150/110	6	Right lower extremity	Worse after 7 months	6
2	46	M	6†	228/174	170/105	4	Right hip	..	10
3	47	M	9	219/130	210/130	4	Both ankles, right hip and knee	Worse after 5 months	3‡
4	53	M	9§	225/125	220/120	4	Feet and ankles	Worse after 5 months	Unknown, complete recovery
5	55	F	4	270/130	236/120	20	Forearms, wrists, left knee	..	Unknown, complete recovery
6	66	F	6¶	220/110	206/110	3	Ankles	..	7
7	50	F	6	218/134	190/110	4	Feet and ankles	Improved after 18 months	12
8	62	M	6	160/90	164/90	3	Left lower extremity	Worse after 2 months	4
9	68	F	6	190/100	184/100	5	Feet and ankles	Worse after 4 months	5
10	60	M	6	..	190/108	6	Right foot and ankles	..	5
11	66	F	6	..	188/98	5	Left lower extremity	Worse after 7 months	3‡

* Interval between beginning of administration of potassium thiocyanate and onset of symptoms.

† Five days a week.

‡ Improving, but not completely asymptomatic.

§ Six days a week.

¶ Four days a week.

over a period of several months was noted in the 7th case under such measures, and the rate of improvement was accelerated when the drug was stopped.

Cessation of potassium thiocyanate therapy was followed by relief in every one of the 11 cases whether or not specific measures of treatment were used. Improvement was generally evident in 2 to 3 months; recovery was complete in 5 to 7 months. Administration of the drug was resumed in 4 instances. In 2 cases there was no recurrence of symptoms or of osteoporosis. Symptoms recurred in the other 2 but were again relieved when thiocyanate therapy was once more discontinued.

Laboratory Data. The laboratory findings are listed in Table 2. The blood thiocyanate levels shown were those present at the time of admission with the osteoporosis. The thiocyanate levels in general varied considerably in different patients and in the same patient from time to time.

serum calcium level, determined in 5 instances, was within normal limits in 3 and slightly below normal in 2. In one of these, Case 9, a urinary Sulkowitch test gave a Grade 4 reaction (graded on the basis of 1 to 4, in which 1 represents the least, and 4 the greatest concentration of calcium).

Report of Cases. The numbers of the following 3 cases, which are reported in detail, correspond to the case numbers in Tables 1 and 2.

CASE 2. A white man, 46 years of age, registered at the clinic in January, 1939, for consultation regarding hypertension. His blood pressure was 228 mm. of mercury systolic and 174 diastolic. Potassium thiocyanate therapy was instituted; the dosage was 6 gr. (0.4 gm.) a day, 5 days a week.

He returned July 18, 1939, complaining of localized pain in the right hip. Its onset in May had been quite sudden, and the pain had been continuous and progressive since then. Only the use of crutches had provided some relief.

The patient appeared in moderate distress and walked with a noticeable limp. Atrophy

TABLE 2.—OSTEOPOROSIS OCCURRING DURING POTASSIUM THIOCYANATE THERAPY FOR HYPERTENSIVE DISEASE: BLOOD CHEMICAL FINDINGS

Case	Mg. per 100 cc.					Alkaline phosphatase, Bodansky units
	Cyanates	Urea	Serum calcium	Serum phosphate	Uric acid	
1	4.7	34				
2	9.3	24	10.0	2.9	3.5	3.7
3	3.8	22				
4	8.9	28	9.8	..	4.4	
5	7.6	24				
6	11.9	28				
7	8.5	28	3.3	
8	11.6	30	8.7	2.2	..	2.8
9	9.8	30	8.7	3.1		
10*	30				
11	4.4†	38	9.4	2.8	1.8	3.1

* Drug had recently been discontinued; no level ascertained.

† Level 2 weeks after drug had been discontinued.

The value for blood urea was within normal limits in all cases. The blood uric acid level was normal in 4 cases. The sedimentation rate was elevated in 2 of the 11 cases, but remained so after complete recovery in both. The serum phosphate level was determined in 4 patients and the blood alkaline phosphatase in 3. All were within the usual range of normal. The

of the right buttock and quadriceps was noted. His blood pressure was 170 mm. of mercury, systolic, and 105, diastolic. Roentgenograms of the pelvis and right femur revealed marked osteoporosis of the right acetabulum and upper part of the femur. The blood chemical findings are given in Table 2.

Potassium thiocyanate therapy was discontinued; treatment consisted of the oral

administration of calcium and viosterol and the patient continued to use crutches. In October, 1939, he was much improved. A roentgenogram at that time revealed some residual osteoporosis.

Recovery was complete in May, 1940, and roentgenograms revealed no osteoporosis. Potassium thiocyanate therapy was resumed in November, 1940, and continued until the patient died more than 5 years later. There was no return of symptoms.

CASE 3. A white man, 47 years of age, was admitted to the clinic in October, 1942, complaining of severe headaches. His blood pressure was 219 mm. of mercury, systolic, and 130, diastolic. Nine grains (0.6 gm.) daily of potassium thiocyanate was prescribed, beginning October 20, 1942.

In July, 1943, he was readmitted. His headaches had improved. However, he complained of pain and swelling in the right knee which had begun early in 1943 (Fig. 1) and which had been followed in a month by similar symptoms in the right ankle. Heat, massage and sun-lamp therapy had failed to

provide any relief. He had discontinued use of the thiocyanates in April and had had the ankle strapped in May; shortly thereafter he noted improvement. He had then resumed thiocyanate therapy and his symptoms returned. At that time the symptoms were located in the right knee and hip.

General physical examination gave essentially negative results except for the hypertension and a limp favoring the right leg. His blood pressure was 210 mm. of mercury, systolic, and 130, diastolic. Roentgenograms of the right hip and knee revealed moderate diffuse osteoporosis (Fig. 2). The blood cyanate level was 3.8 mg. per 100 cc.; the blood urea was 22 mg. per 100 cc.

Baking, massage and exercises for hip, knee and ankle were prescribed. The dosage of potassium thiocyanate was increased to 12 to 15 gr. (0.78 to 1 gm.) daily. The patient wrote in September, 1943, that he was worse and that both ankles were now involved. Potassium thiocyanate therapy was once more discontinued. A letter from the patient in December, 1943, stated that he



FIG. 1.—(Case 3.) Appearance of right knee on March 8, 1943, 5 months after potassium thiocyanate therapy had been started.

was much better and was steadily improving.

CASE 9. A white woman, 68 years old, was seen at the clinic in January, 1945, because of severe headaches. Her blood pressure was 190 mm. of mercury, systolic, and 100, diastolic. Potassium thiocyanate therapy was begun at that time. The dosage varied, but averaged 6 to 9 gr. daily.

The roentgenograms revealed diffuse osteoporosis of both feet and ankles (Fig. 3a). The blood chemical findings are given in Table 2. The reaction to the urinary Sulzowitch test on a 24 hour specimen was graded 4.

The patient was instructed to discontinue all therapy, including the use of thiocyanates



FIG. 2.—(Case 3.) Appearance of right knee July 26, 1943. Increased osteoporosis despite intensive local therapy is apparent while the patient was still on potassium thiocyanate.

The patient returned in October, 1945, stating that her headaches were relieved but that her feet and ankles were painful, swollen and stiff. Pain had begun in June, 1945, followed shortly by the stiffness and swelling. Her symptoms had since become progressively worse despite physiotherapy and the use of contrast baths, shoe corrections and elastic bandages.

General physical examination gave essentially negative results except as regards the hypertension and the condition in lower extremities. The blood pressure was 184 mm. of mercury, systolic, and 100, diastolic. Slight diffuse swelling, stiffness and tenderness of both feet and ankles were noted.

as well as measures directed at the osteoporosis. She stated, on her return in April, 1946, that her symptoms had steadily improved and that she was bothered only occasionally. Disappearance of the osteoporosis was evident on roentgenologic examination (Fig. 3b).

Comment. No cause for this syndrome other than thiocyanate therapy could be found. Trauma at the onset was consistently denied. One patient sprained the involved ankle shortly after the initial appearance of symptoms and this sprain markedly aggravated her discomfort. No other therapeutic procedure was instituted

for any significant period of time during the development of the osteoporosis in any case. Concurrent, but probably unrelated, conditions occurred in 2 patients. One consisted of a diarrhea beginning 2 months after the onset of symptoms. The other was a burn of the thumb with secondary infection. Sulfathiazole treatment was administered to the latter patient in the interval just preceding the appearance of symptoms; however, the osteoporosis in this case involved the ankles. No evidence

of renal insufficiency was noted in any of these patients. The possibility of a local vascular accident with overcompensating collateral circulation and hyperemia was suggested as a cause for the osteoporosis. The absence of this syndrome in more than 5000 consecutive patients with hypertension who did not receive potassium thiocyanate makes it extremely unlikely that a complication of the hypertensive disease was the underlying cause of the osteoporosis.

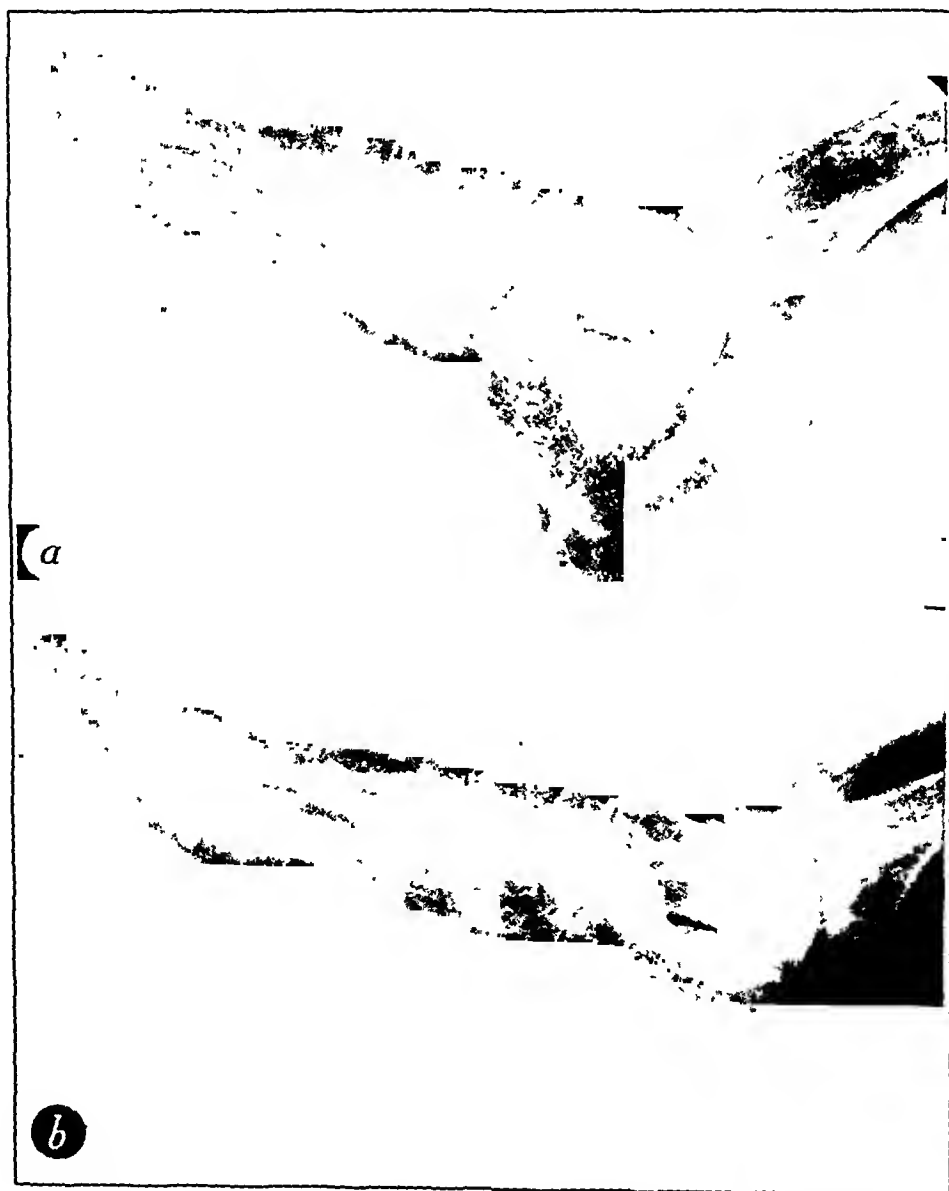


FIG. 3.—(Case 9.) *a*, Osteoporosis of right foot and ankle which occurred while the patient was receiving potassium thiocyanate; the condition continued despite intensive local measures directed at the osteoporosis itself. *b*, Improvement after discontinuance of potassium thiocyanate therapy and of that for osteoporosis.

The following evidence suggests that the osteoporosis was a result of thiocyanate therapy: (1) there was a sufficient time interval between institution of the drug and onset of symptoms; (2) improvement was noted in a reasonable period of time after discontinuance of the drug, whether or not therapy was directed at the osteoporosis; (3) in 6 of the 7 cases the usual specific therapeutic measures failed to halt progression of the osteoporosis so long as potassium thiocyanate therapy was continued; (4) increase in dosage of the drug in one instance resulted in an aggravation of symptoms within a few weeks; and (5) resumption of use of the drug after recovery produced recurrence of symptoms in 2 of 4 cases, with relief after the drug was again discontinued.

A mode of action of the potassium thiocyanate must still be postulated. No marked lowering of blood pressure was noted consistently. The osteoporosis occurred far too infrequently to be the result of a direct action of the drug on bone itself.

Potassium thiocyanate therapy has been used in more than 100 cases of severe migraine without the production of any syndrome such as that of osteoporosis. Evidence at hand at present seems to favor a slight but prolonged interference with calcium metabolism as the mechanism of the production of the osteoporosis. The actual dosage of the drug is small, although it is in excess of those of aluminum and iron which have been recommended in different types of bone malacia. In the presence of adequate calcium intake and normal metabolism, such a slight interference with calcium metabolism would scarcely be sufficient to produce osteoporosis, and it has not occurred in the migrainous patients who represent a younger age group. However, should there be a tendency to a negative calcium balance, which is so often found in individuals of the age group with which this report deals, then any additional deficiency in calcium metabolism could produce such a picture. The finding of subnormal values for serum calcium in 2 cases and of a Grade 4 reac-

tion to the Sulkowitch test in 1 case was further suggestive evidence of this mechanism. Thus all known factors, including the time element both for production of and recovery from this syndrome, the infrequency of occurrence of the syndrome, the dosage of the drug, and the group of individuals dealt with, were consistent with a minor additional interference with calcium metabolism. Further investigation along these lines is being carried out at present.

Regardless of the mechanism of production of osteoporosis, one should be cognizant of the occasional occurrence of this condition and should insure adequate calcium intake in individuals who are taking potassium thiocyanate. The use of this drug in the presence of a fracture may be inadvisable, not as regards union of the fracture, which is a local affair, but because any interference with calcium metabolism in the presence of an increased calcium requirement might precipitate osteoporosis. Potassium thiocyanate therapy may similarly be contraindicated in the presence of bone malacia, such as senile osteoporosis or osteitis deformans, as use of the drug could cause further increase of decalcification and aggravation of symptoms.

Summary and Conclusions. Osteoporosis with arthralgia was noted in 2% of patients receiving potassium thiocyanate therapy for hypertension. No similar syndrome was found in more than 5000 consecutive cases of hypertension in which this drug was not used. Evidence at hand seems to suggest slight and prolonged interference with calcium metabolism as a possible mechanism for production of the syndrome. It appears that adequate calcium intake should be assured for persons who are taking potassium thiocyanate. Use of this drug may be contraindicated in the presence of bone malacia, such as senile osteoporosis or osteitis deformans; likewise its use may be inadvisable in the presence of fracture, not as regards union of the fracture but because any interference with calcium metabolism in the presence of increased calcium requirement might precipitate osteoporosis.

BLOOD VOLUME CHANGES AND AVAILABLE (THIOCYANATE) FLUID SPACE IN SOLDIERS WITH CHRONIC WOUND INFECTIONS AND ASSOCIATED NUTRITIONAL DEPLETION

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DURING World Wars I and II, studies correlating blood volume changes with the clinical signs of shock have been carried out. Few data are available concerning the changes in blood volume which occur in individuals with chronic wound infections and extensive losses in body weight, conditions often present weeks or months after severe trauma. Recent observations by Lyons¹⁶ have led him to conclude that such patients show: (a) an increased interstitial (thiocyanate) fluid volume as compared with standards for their weight before injury, (b) a reduction of 1.5 to 2 liters in blood volume, (c) a deficit in the total amount of circulating hemoglobin. Gregersen¹¹ has observed similar cases in which the blood volume, evaluated in terms of normal body weight, was reduced 30 to 40%.

Our experience with traumatically injured soldiers who had chronic wound infections and considerable weight loss has indicated that such patients are particularly susceptible to shock after surgical procedures. Although many of these individuals have weight losses ranging between 15 and 30 kilos, their concentrations of plasma proteins and red cells differ very little from those shown by normal man. It is apparent that the latter values are not good indices of changes in the blood volume. In 1945 the present investigation was undertaken to measure the blood volume and to determine the state of dehydration in battle casualties with chronic

wound infections. It was hoped that such a study might result in a better guide for therapeutic management than that afforded by routine laboratory methods.

Method and Procedure. A group of 27 wounded male soldiers varying between 19 and 40 (average 22.2) years of age was studied. All had undergone a period of strenuous military training and were regarded as normal prior to injury. Several were paratroopers, the rest being infantrymen. The results obtained upon these patients are compared with those obtained from a group of 34 German prisoners of war whose ages ranged between 16 and 43 (average 26.5) years of age. These volunteers who were selected at random had been fed adequate American rations for over a year and were engaged in manual labor.

In all instances the determinations were made before breakfast with the subjects in a basal, post-absorptive state. Most of the patients were confined to their beds. In any event, the measurements were made under basal, post-absorptive conditions. None of the patients showed any evidence of cardiac failure or of peripheral vascular collapse. All were conscious, mentally coherent, and able to respond satisfactorily to questions. In the case of recent arrivals in the hospital, intravenous therapeutic procedures were postponed until some of our tests were completed. The entire group of normal subjects, and 15 of the 27 patients (Cases A1 to A15, Tables 2 and 3) were accurately weighed on a calibrated platform scale. The other 12 patients (Cases B16 to B27) were included although their clinical conditions or partial immobilization in fixed plaster casts prevented

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accurate body weight determinations. In these the weight loss was estimated, and only those in which the loss was judged to be 15 kilos or more were studied.

The plasma volume was measured with the blue dye, T-1824, using the simplified method described by Gregersen¹² in which the dye concentration is estimated with the Nickerson Decade Photometer. In most of the patients, the arms and forearms were repeatedly soaked with warm, wet towels, and both hands were immersed in warm water for 10 minutes prior to venipuncture. The skin at the site of venipuncture was first infiltrated with 1% novocaine containing no epinephrine. In individual instances in which both antecubital veins were not available, one of the external jugular veins was used.

In patients in whom both plasma volume and available (thiocyanate) fluid volume determinations were made, the procedure was carried out as follows:¹³ after anesthetizing the skin, one antecubital vein was punctured with a 19-gauge needle and a dye-free blood sample was collected without stasis. Six cc. of blood were now collected in each of 2 tubes, one containing a small amount of mineral oil, the other coated with a thin film of dry heparin.* Through the same needle, 15 cc. of a 5% solution of sterile sodium thiocyanate† in an accurately calibrated syringe, were injected. The syringe was washed 3 times by drawing and reinjecting blood. Through the same needle 5 cc. of T-1824 from ampoules‡ containing a known amount of dye solution of known concentration were injected, the syringe rinsed as described above, the time recorded, and the needle withdrawn. Exactly 10 minutes later a sample (6 cc.) of blood was withdrawn without stasis from the opposite antecubital vein and transferred to a 10-cc. tube containing heparin for determination of the plasma concentration of the dye. In 5 patients 6 cc. of blood were withdrawn

without stasis at the end of 1, 2, and 3 hours and transferred to test tubes containing a small amount of mineral oil for the estimation of the serum concentration of sodium thiocyanate. Since the 2 and 3 hour samples did not differ from the 1 hour sample, the practice of drawing blood at the end of 2 and 3 hours was discontinued in the subsequent measurements. The heparinized blood (dye-free and 10 minute dye-tinged) samples were transferred to separate 4-cc. hematocrit tubes (10 mm. x 8 mm.) and centrifuged for 30 minutes at 3000 r.p.m. The hematocrit values obtained in the dye-free and dye-tinged samples agreed to within 2%, affording confirmatory evidence of the absence of hemostasis in the collection of the blood. Hemolyzed samples were discarded, the plasma volume determination being repeated. After centrifugation the plasma of the 10 minute dye-tinged sample was read at 624 m μ . in 10 mm. cells against a dye-free blank with the Nickerson Decade Photometer. The optical density was noted, and the plasma volume read from the appropriate table.¹² The total blood volume was calculated from the equation:

$$\text{Total blood volume (cc.)} = \frac{\text{Plasma volume (cc.)}}{1 - \text{hematocrit}}$$

The plasma volume determined from a single 10 minute point is, on the average, 3.2% greater than that measured from time-concentration curves.¹⁹ For our purposes, the method is adequate because the error is slight compared with the changes in plasma volume measured on our patients. Moreover, we have compared our results on injured soldiers with values obtained by the same method on the control group.

The available (thiocyanate) fluid volume was measured as follows: To 2 cc. of serum from the 1 hour blood sample, 2 cc. of 2% trichloroacetic acid were added. The resultant mixture was centrifuged at 3000 r.p.m. for 10 minutes, and to 2 cc. of the supernatant

* Five mgs. of pure heparin were dissolved in a small amount of distilled water in 10 cc. test tubes which were placed in a tilted position in a desiccator and periodically rotated until dry, so that a thin film of heparin was left coated upon the inner surface of each tube.

† The ampoules of 5% sterile sodium thiocyanate were supplied by the Warner Institute of Therapeutic Research, N. Y. C.

‡ The ampoules containing exactly 5 cc. of a carefully standardized solution of T-1824 were supplied by the Warner Institute of Therapeutic Research, N. Y. C. This was rechecked for accuracy of standardization according to procedure outlined by Gregersen.¹²

MacAlaster Bicknell Co., Cambridge, Mass.

fluid were added 2 cc. of ferric nitrate solution. The red color thus developed was read immediately in a Coleman Junior Spectrophotometer set at 460 $m\mu$. against the similarly treated control sample. The available (thiocyanate) fluid volume was calculated from the formula given below.†

The plasma protein concentrations were determined by the falling drop method of Barbour and Hamilton,¹ using the formula of Weech *et al.*³⁰ The hemoglobin determinations were made with the Fisher electrohemometer.¹⁸

The total blood volume calculated from the plasma volume (dye method) and the venous hematocrit has been regarded as erroneous by some investigators,^{7,25,26} owing to differences between the values for the venous hematocrit reading and that found for the total body hematocrit. This difference is said to result from the unequal distribution of red cells in the various vessels of the vascular system. However, the report of Hopper, Tabor, and Winkler¹⁴ shows that the average blood volumes measured simultaneously by dye and carbon monoxide methods in man and dog are almost identical. Further evidence that the central hematocrit reading does not differ markedly from the total body hematocrit has been obtained recently by Root, Roughton, and Gregersen²¹ who also obtained close agreement between the blood volumes obtained by the simultaneous measurement with dye and carbon monoxide. On the basis of this evidence, we feel that the total blood volume can be calculated from the plasma volume and the venous hematocrit reading.

The available (thiocyanate) fluid volumes were calculated from the uncorrected formula shown above. Although this ignores the fact that thiocyanate diffuses into the erythrocytes and that it is present in serum partly in bound form,¹⁵ we feel that useful results can be obtained with this method.

Results. NORMAL GROUP. The results obtained on 34 normal individuals are shown in Table 1. These include determinations of plasma volume, available thiocyanate fluid volume, venous hematocrit reading, hemoglobin value, plasma protein concentration, and calculations of total blood volume, red cell volume, total circulating hemoglobin, and total circulating

plasma proteins. Distribution curves based on the individual values for the plasma volume and blood volume expressed as cc. per cm. height, cc. per kg. body weight, and as liters per sq. m. body surface indicate, in agreement with the results of Rowntree and Brown,²⁴ that although the plasma and blood volume correlate well with height and weight, the correlation with body surface is better. The mean values for the various measurements, with their respective standards of deviation and coefficients of variation are given at the bottom of Table 1. Distribution curves of the various measurements are shown in Figure 1.

The plasma volume of the 34 normal males ranged from 1.31 to 2.20 liters per sq. m., the mean being 1.76 liters per sq. m. (S.D. = 0.20). In terms of cc. per kg. body weight, the values are 32.4 to 56.9, mean 45.3 (S.D. = 5.5). The total blood volume showed a greater range, varying from 2.14 to 4.10 liters per sq. m. of body surface. The mean value for the entire group was 3.12 liters per sq. m. (S. D. = 0.36). Expressed in terms of cc. per Kg. of body weight, these values become 57.5 to 106.0, mean 80.1 (S. D. = 16.5).

The blood volume and other measurements shown in Table 1 agree well with similar determinations reported by other investigators.^{9,20,29}

In agreement with the report by Crandall and Anderson,⁷ our results indicate that the available (thiocyanate) fluid volume correlates better with surface area than with body weight. The volumes for the 34 normal subjects (Fig. 1, G) ranged from 8.1 to 11 liters with a mean value of 9.8 liters per sq. m. (S.D. = 0.61).

WOUNDED SOLDIERS. The revised diagnoses of the 27 patients studied are shown in Table 2. This table also includes a statement of the nature of the wound sustained. The individual patients have been assigned the same symbol in Table 2 as in Table 3. Since from 7 to 24 weeks had elapsed between the time of injury

† Available fluid in liters = $\frac{\text{Total amount of NaCNS injected in gm.} \times 100}{\text{mg. NaCNS/100 cc. serum after equilibrium is established.}}$

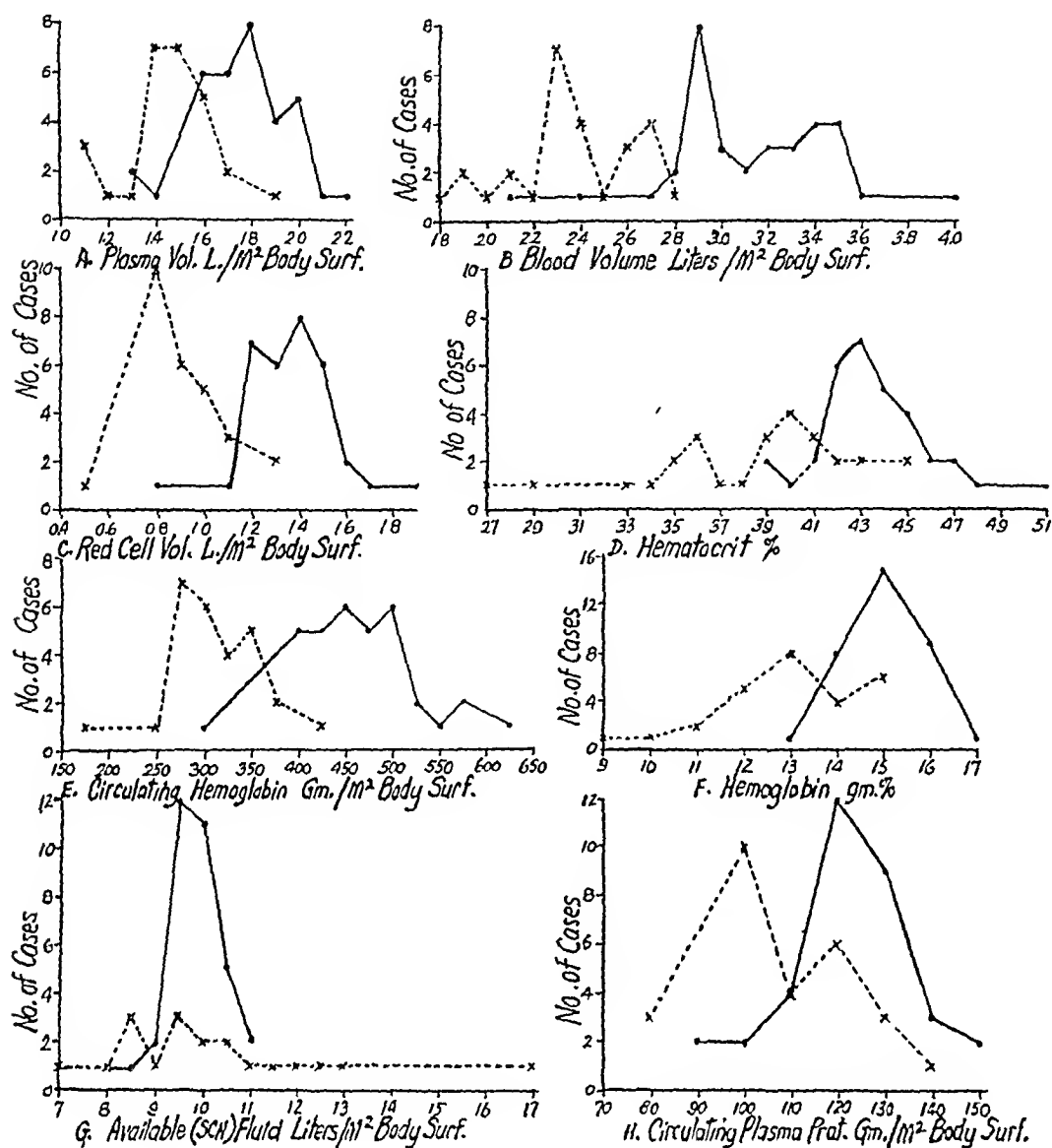


FIG. 1.—Distribution curves from body fluid data obtained from the 27 wounded soldiers studied compared with corresponding data from 34 normal male controls. The closed circles represent individual values in the normal control group. The crosses represent individual values in the patient group.

and the time at which our observations were made (see Table 2), many of our patients had recovered from the effects of some of the initial wounds. Others had developed various complications, some of which were remotely associated with and of graver import than the initial injury. Hence, the original diagnoses listed in such accompanying tags, records, and charts as were available to us have been revised to conform with the clinical status of each patient at the time he was studied (Table 3).

Practically all of the wounds were of the complex polymicrobial type similar to those described by Lyons¹⁶ and Pulaski and Sprinz.²² The extent and character of the anatomical involvement were also extremely varied (see Table 2). All of our patients had had surgical attention, had received either sulfonamides, or penicillin, or both, as well as variable amounts of plasma or whole blood at different medical installations. Accurate data concerning previous transfusions or other parenteral

TABLE 2.—DIAGNOSES OF THE 27 WOUNDED SOLDIERS REPORTED IN THIS STUDY (EACH SYMBOL IN TABLES 2 AND 3 REFERS TO THE SAME PATIENT)

Case	
A1	Wounded 21 weeks previously, struck by mast of ship attacked by bombers; simple compression fracture of 1st lumbar vertebra; no cord injury; traumatic subdural cyst, cauda equina (healed); multiple, large decubitus ulcers; acute bilateral pyelonephritis; chronic cystitis (suprapubic cystotomy).
A2	Accidentally injured 21 weeks previously with resulting compression of the cauda equina, and paraplegia secondary to fracture and compression of 1st lumbar vertebra; compound linear fracture right frontal bone, healed; simple fracture, 5, 6 right ribs, healed; contusion right kidney, healed; nephrolithiasis with acute pyelonephritis, bilateral; chronic cystitis (suprapubic cystotomy); multiple decubitus ulcers.
A3	Wounded by shell fragments 20 weeks previously; fracture, compound, comminuted of 2, 3, 4, 5 left metatarsals with no evidence of callus formation after 4 months; fracture, simple, right humerus, healing; partial paraplegia secondary to comminuted fracture (healed), 4th lumbar vertebra; chronic cystitis (suprapubic cystotomy); multiple, large granulating decubitus ulcers.
A4	Wounded by bullet 17 weeks previously; penetrating bullet wound right chest; fracture dislocation 4, 5, 6 thoracic vertebrae; severe partial traumatic myelitis and paraplegia with sensory loss up to D9; chronic empyema (treated by open drainage) and bronchopleural fistula right chest; chronic cystitis (suprapubic cystotomy); multiple decubitus ulcers.
A5	Wounded 10 weeks previously by shrapnel; perforating wound severe entering left flank and with exit at right flank with resultant laceration of cecum (cecotomy and appendectomy performed on date of wound); incomplete compound comminuted fracture left ilium with chronic osteomyelitis; fecal fistula left flank.
A6	Wounded 11 weeks previously by shrapnel; wound, suppurating, soft tissues right gluteal region with draining abscess, deep; no fracture.
A7	Wounded by shrapnel 14 weeks previously; suppurating wound soft tissues right deltoid region; no bone injury; postdiphtheritic polyneuritis and generalized motor paralysis.
A8	Wounded by shrapnel 9 weeks previously; multiple penetrating wounds (healed) left foot, leg, thigh and gluteal region, right thigh, and left forearm; compound complete fracture (healing) left radius; paralysis left ulnar nerve; purulent drainage from fistulous tract, right pararectal region, secondary to lacerated wound with large perforation posterior rectal wall.
A9	Wounded 22½ weeks previously by shrapnel; chronic osteomyelitis, shaft right femur, secondary to compound comminuted fracture; large chronic suppurating wound right thigh.
A10	Wounded by shrapnel 8 weeks previously; chronic, deep, draining abscess left thigh extending into Hunter's canal; paralysis left femoral nerve; simple, incomplete fracture neck of left femur; simple comminuted fractures 8, 9 right ribs; suppurating wound right flank (5 by 10 cm.).
A11	Wounded by bullet 10½ weeks previously, perforating wound abdomen with lacerations of colon, mesentery and jejunum (colostomy present, intestinal lacerations healed); comminuted fracture 4th, 5th lumbar vertebrae; traumatic myelitis, with paraplegia; chronic retroperitoneal abscess; osteomyelitis, ilium, left; acute pyelonephritis, right; chronic cystitis (suprapubic cystotomy).
A12	Wounded by bullet 15 weeks previously; perforating wound abdomen with 4 perforations of ilium (healed); suppurating wounds left flank, left leg; draining psoas abscess, left.
A13	Wounded by shrapnel 21 weeks previously; penetrating wound right flank with shell fragment lodged at 4th lumbar vertebra; fecal fistula right flank to ascending colon; draining subdiaphragmatic abscess, right; laceration nerve roots (4 and 5 lumbar and 1st sacral) with secondary paresis; chronic cystitis with bilateral ascending pyelonephritis.
A14	Wounded by shrapnel 19 weeks previously; penetrating wound, right gluteal region; chronic osteomyelitis, head of right femur and acetabulum secondary to compound comminuted fracture; pyoarthritis right knee joint; fecal fistula descending colon; retroperitoneal abscess; colostomy.
A15	Wounded 14 weeks previously by bullet, left flank with perforation of stomach and injury to pancreas and kidney (all healed) except for draining sinus, left flank.
B16	Wounded 14 weeks previously by shell fragment; chronic osteomyelitis, right femur, secondary to compound comminuted fracture.
B17	Wounded by bomb fragment 12 weeks previously; perforations of stomach (healed); perforation of hepatic flexure (externalized as colostomy); double barrel jejunostomy done for intestinal obstruction; intra-abdominal mural abscess; perilepatitis; chronic peritonitis, bronchopneumonia; determinations done 3 weeks before death.
B18	Wounded by bomb fragments 12 weeks previously; chronic osteomyelitis (resolving) secondary to compound fracture, left tibia and fibula.

TABLE 2.—DIAGNOSES OF THE 27 WOUNDED SOLDIERS REPORTED IN THIS STUDY (EACH SYMBOL IN TABLES 2 AND 3 REFERS TO THE SAME PATIENT)—CONTINUED

Case	
B19	Wounded by mine fragments 19 weeks previously; chronic osteomyelitis, ischii, pubes, sacrum, coccyx, and necks of both femurs, secondary to compound comminuted fractures; chronic cystitis (suprapubic cystotomy); suppurating wounds, right thigh; multiple decubitus ulcers.
B20	Wounded by bullet 24 weeks previously; penetrating gunshot wound resulting in fracture, 7th cervical vertebra, with traumatic myelitis and complete paralysis below C7; clean granulating stump left leg after amputation below knee 1 month previously for gangrene; multiple large decubitus ulcers; chronic cystitis (suprapubic cystotomy) tests done 4 days before death (preceded by unexplained convulsions).
B21	Wounded 15 weeks previously by bullet; penetrating wounds, buttocks and rectum; colostomy closed; wounds granulating slowly.
B22	Accidentally injured in jeep 7 weeks ago; compound septic necrosis left knee joint and simple fracture rim of left acetabulum.
B23	Wounded by shell fragment; wounds soft tissues right leg (granulating slowly); no fracture.
B24	Wounded by shell fragment 16 weeks previously with infected wound soft tissues left leg; amputation stump right leg (healed).
B25	Wounded by shell fragments 7 weeks previously with granulating wounds right ankle, elbow and shoulder; fracture, right ankle (uniting).
B26	Wounded 12 weeks previously by shell fragment; chronic osteomyelitis right femur, tibia, fibula and cuneiform bone and 1st metacarpal secondary to multiple compound comminuted fractures.
B27	Wounded by shell fragment 19 weeks ago; chronic osteomyelitis right femur, tibia and fibula and left tibia, secondary to multiple compound comminuted fractures; suppurative arthritis and synovitis, both knee joints.

therapy were generally incomplete. Eight of our patients had paraplegia. Measurements of the height and weight before injury were available for all the patients, from which the normal surface area could be determined in the usual way.³ The body fluid measurements have been computed in terms of liters per sq. m. of normal body surface. The results of the measurements of plasma, total blood, red cell, and available fluid volumes are shown in Table 3. Hematocrit readings, and hemoglobin and plasma concentration also appear in this table. For comparison with the results obtained in the normal group, the frequency distribution curves of the body fluid measurements of the patient group are presented in Figure 1.

We have compared the mean total volume measurements of plasma, total blood, red cells, and available thioeyanate fluid of the patient group with estimated normal values obtained by multiplying the mean normal surface area of the patients by the mean volume per sq. m. of body surface measured in the normal group. The mean hematocrit readings, and hemoglobin and plasma protein concentrations of the 27

patients are compared with the corresponding mean value of the 34 normal males. Their values are given in Table 4. In column 5 of this table, the mean changes from the estimated normal appear, and in column 6 is given the percentage increase or decrease from the normal. The statistical significance of the change (column 7) is expressed by dividing the values of column 5 by the standard error.

Blood Volume. The average plasma volume of the 27 patients was 2760 cc. which is 580 cc. or 17.3% less than the mean estimated normal value. Similarly based comparisons for the total blood and red cell volumes of these patients showed an even greater decrease for the mean total blood volume amounting to 1430 cc. (24.2%), and a reduction in the mean red cell volume equal to 815 cc. (31.6%). The reduction in total blood volume is the result of decreases in both plasma volume and red cell volume, but the decrease in the latter is 1.8 times that shown by the former. The average hematocrit of our patients was 38.4%, which is 11.7% less than the mean hematocrit for the control group. The reduction in the mean red cell

TABLE 3.—BODY FLUID DATA OBTAINED FROM 27 SOLDIERS WITH CHRONIC WOUND INFECTION, NUTRITIONAL DEPLETION, AND WEIGHT LOSS (EACH SYMBOL IN TABLES 2 AND 3 REFERS TO THE SAME PATIENT)

Case	Age	Height (cm.)	Weight		Surface area		Plasma volume		Blood volume		RBC volume		Plasma protein		Hemoglobin		Available fluid			Hematocrit (%)
			Normal (kg.)	Loss (kg.)	Normal (M ²)	Present (M ²)	Total L.	Normal S.A. (L/M ²)	Total L.	Normal S.A. (L/M ²)	Total L.	Normal S.A. (L/M ²)	Gm. %	Total circ. (gm.)	Gm. %	Total circ. (gm.)	Total L.	Normal S.A. (L/M ²)	Present S.A. (L/M ²)	
A1	21	170	63.5	31.5	1.71	1.38	1.90	1.09	3.22	1.85	1.32	0.70	8.8	107	14.7	473	18.0	10.3	14.1	41.0
A2	21	170	57.0	40.0	1.65	1.42	2.20	1.33	3.44	2.08	1.24	0.75	8.0	170	12.7	437	13.8	8.4	6.7	36.0
A3	19	172	64.5	38.5	1.80	1.41	4.16	1.41	4.16	2.30	1.56	0.88	6.8	173	14.7	611	10.0	8.6	11.0	37.5
A4	31	177	66.0	41.5	1.81	1.53	2.80	1.55	4.21	2.31	1.44	0.80	7.0	195	12.1	513	23.0	12.7	14.0	31.0
A5	30	177	82.0	53.5	1.98	1.60	4.80	1.46	4.75	2.36	1.60	0.81	7.2	206	12.3	680	23.0	11.6	14.0	33.5
A6	21	168	78.5	52.5	2.02	1.71	2.80	1.39	4.75	2.36	1.03	0.67	7.1	202	13.0	637	26.2	10.0	11.8	41.0
A7	23	161	70.5	48.0	1.89	1.71	2.80	1.22	3.70	1.93	1.60	0.85	7.3	182	11.5	566	17.6	9.3	16.3	41.6
A8	26	177	72.5	48.0	1.92	1.61	2.10	1.00	3.70	1.93	1.60	0.81	7.7	204	13.2	509	13.3	7.0	8.3	43.0
A9	20	177	72.5	53.5	1.99	1.73	2.65	1.35	4.31	2.18	1.53	0.77	7.2	276	9.6	423	16.2	8.3	6.4	38.5
A10	24	179	81.0	58.0	2.02	1.69	5.75	1.88	5.38	2.66	1.83	0.77	5.9	165	14.1	718	10.6	8.2	9.4	29.6
A11	24	173	68.0	45.0	1.82	1.53	3.70	1.39	5.06	2.52	1.29	1.13	8.0	210	10.6	437	18.4	10.5	12.5	45.0
A12	32	170	70.5	43.0	1.80	1.46	4.12	1.48	4.12	2.42	1.42	0.78	7.6	232	12.0	506	16.1	10.1	12.0	31.5
A13	23	166	78.5	49.5	1.67	1.61	3.97	1.72	4.92	2.72	1.82	1.02	8.2	239	9.2	365	11.7	8.7	9.6	27.0
A14	19	170	70.5	53.0	1.83	1.63	4.30	1.42	4.30	2.31	1.70	0.63	8.2	213	13.2	568	14.7	13.0	14.6	41.5
A15	23	172	63.0	43.2*	1.73	1.53	3.80	1.60	4.79	2.71	1.99	1.14	0.0	163	13.6	651	22.7	13.0	14.6	42.0
A16	23	172	69.5	50.0*	1.82	1.60	3.80	1.54	5.09	2.80	2.29	1.25	7.5	210	15.2	775	22.5	11.8	14.0	38.5
A17	22	175	73.0	50.0*	1.91	1.60	3.00	1.57	4.89	2.56	1.83	0.99	7.3	219	13.3	619	33.2	17.0	26.7	35.0
A18	28	173	81.8	50.0*	1.96	1.60	3.00	1.53	4.61	2.31	1.61	0.82	0.8	201	11.2	515	18.0	9.5	11.1	40.0
A19	20	177	73.1	51.7*	1.91	1.62	2.70	1.41	4.50	2.36	1.80	0.61	7.2	195	14.0	730	17.9	9.4	10.9	33.0
A20	26	177	70.0	51.7*	1.90	1.63	4.59	1.63	4.59	2.42	1.49	0.79	7.4	230	11.5	598	13.9	9.4	10.9	40.0
A21	22	182	77.1	51.7*	1.87	1.68	4.47	1.47	4.58	2.41	1.83	0.98	8.8	212	13.2	630	39.0	11.8	14.0	38.5
A22	23	182	75.0	50.0*	1.93	1.69	5.15	1.85	5.15	2.91	1.85	0.95	7.5	218	12.9	637	43.0	11.1	14.0	40.0
A23	23	182	77.1	51.7*	1.93	1.69	5.15	1.85	5.00	2.56	2.15	1.70	7.6	216	12.9	615	39.5	11.1	14.0	40.0
A24	23	180	83.8	63.5*	2.21	1.81	3.05	1.36	5.04	2.90	1.99	0.89	7.5	229	13.2	665	39.5	11.1	12.0	40.0
A25	20	182	86.5	68.3*	2.01	1.87	3.30	1.63	5.50	2.70	2.70	1.32	7.1	234	12.5	689	22.7	11.1	12.0	40.0
Total			1683.0	1370.9	611.1	43.68	71.55	36.22	120.73	63.53	40.71	21.62	290.9	552.3	350.0	15.810	308.0	195.8	229.7	1032.5
Mean			67.3	50.8	22.8	1.62	2.70	1.45	4.49	2.30	1.75	0.91	7.4	205	15.0	585	19.1	10.3	12.1	38.4
Standard deviation									0.61		0.39		0.7	31.4	1.5	97.5	4.5			4.3
Coefficient of variation									13.6		22.3		8.9	15.3	11.6	10.7	23.2			11.3

* S. A. = Surface area.
* Estimated weight

* S.A. = Surface area.
* Estimated weight

TABLE 4.—MEAN BODY FLUID MEASUREMENTS FOR THE WOUNDED GROUP REPORTED AND THE RESPECTIVE CHANGES FROM THE ESTIMATED MEAN NORMAL BODY FLUID VALUES FOR THIS GROUP

Measurement	No. of cases	Mean measurement in wounded group studied	Mean estimated normal values*	Mean change in wounded group	Change in wounded group (%)	Difference divided by standard error
Plasma volume	27	2760 cc.	3340 cc.*	-580 cc.	-17.3	6.3
Blood volume	27	4490 cc.	5920 cc.*	-1430 cc.	-24.2	5.6
RBC volume	27	1750 cc.	2565 cc.*	-815 cc.	-31.6	10.0
Available fluid volume	19	19,400 cc.	18,500 cc.*	+900 cc.	+4.9	0.72
Circulating hemoglobin	27	585 gm.	890 gm.*	-305 gm.	-34.2	14.0
Circulating plasma protein	27	205 gm.	235 gm.*	-30 gm.	-12.8	4.8
Hematocrit	27	38.4%	43.5%†	-5.1%	-11.7	6.0
Hemoglobin	27	13.0 gm.%	15.0 gm.%†	-2.0	-13.3	6.9
Plasma protein	27	7.4 gm.%	6.9 gm.%†	+0.5	+5.0	3.3

* The estimated value is obtained by multiplying the mean normal surface area of the cases studied by the corresponding mean normal measurement per sq. m. body surface obtained from the data on the 34 normal males in Table 1.

† Mean normal values observed in the 34 normal males.

volume is therefore 2.7 times the decrease shown by the mean hematocrit. The mean hemoglobin concentration of the patient group was 13 gm. per 100 cc., or 13.3% less than the value for the control group. The mean circulating hemoglobin in our patients was 585 gm. This value is 305 gm. or 34.2% less than the mean estimated normal value. The reduction in the mean circulating hemoglobin is therefore 2.6 times that shown by the reduction in the mean hemoglobin concentration. The values in Table 3 (column 7) indicate that the above observations are statistically significant.

Available (Thiocyanate) Fluid Volume. Available (thiocyanate) fluid volume measurements were made in 19 of the 27 patients studied (Table 3). The volumes obtained when based on the normal surface area of these patients ranged from 7 to 17 liters per sq. m. In 4 cases, the volumes observed were more than 2 standard deviations below the mean normal value. The lowest value was observed in Case A8 whose available (thiocyanate) fluid volume was 7 liters per sq. m. In 6 cases, the available (thiocyanate) fluid volume per sq. m. was more than 2 standard deviations above the mean value for our normal group. Of these 6 cases, 5 showed volumes ranging from 11 to 13 liters per sq. m., while 1 case (B20) had 17 liters of available fluid per sq. m. The average total available (thiocyanate) fluid volume of the 19 patients measured was 19.4 liters which is 0.9

liters or 4.9% above the mean estimated normal value (Table 3). This increase is however, not statistically significant.

Analysis of the individual total available (thiocyanate) fluid volumes in terms of the body weight of each patient at the time this study was made show that 8 of the 19 cases measured presented volumes which were in excess of 40% of their body weight, while 4 of the 8 cases (A1, A4, B17, B20) had volumes equivalent to more than 50% of their body weight. The latter were extremely ill, febrile, and cachectic, and the total available (thiocyanate) fluid volumes observed in them were markedly elevated in comparison with the mean available (thiocyanate) fluid volume found in our normal controls which was equivalent to 25% of the body weight. The measurements in Cases A1, B17 and B20 were made 11, 22 and 3 days prior to death respectively. Two months after the first available fluid determination, a second one was made on Case A4 following marked improvement and the establishment of a positive nitrogen balance. Although this patient had gained only 3.5 kg., his total available (thiocyanate) fluid volume had decreased from 23 liters which was equal to 51.7% of his body weight, to 16.4 liters, a value equal to 34% of his body weight.

Circulating Plasma Proteins. Although weight losses of 14.5 to 32 kg. were observed in the 27 patients studied, the average plasma protein concentration for the entire group was 7.4 gm. per 100 cc.

(S.D. ≈ 0.7) (Table 3) which is 5% more than the mean plasma protein concentration for the control group. Plasma protein values below 6.5 gm. per 100 cc. were observed in 2 cases, while values above 8 gm. per 100 cc. or more were present in 6 cases. The average total circulating plasma protein in the 27 patients was 205 gm. (S.D. ≈ 31.4) which is 30 gm., or 12.8% less than the mean estimated normal value. The linear correlation of the plasma volume to total circulating plasma protein in our normal controls is shown in Figure 2. From the same figure, it is apparent that values for the plasma volume in our 27 patients are generally below normal, although they tend to be disposed along the same axis of drift displayed by the plotted values for the normal control group.

Discussion. Patients with chronic wound infections, nutritional depletion, and anemia show a 24.2% reduction in blood volume as compared with the estimated mean normal value. This is the result of a 17.3% decrease in plasma

volume and a 31.6% reduction in red cell volume. The condition may be described as an oligocythemic hypovolemia. According to Stead and Ebert²⁷ the blood volume of normal subjects with a relatively constant arterial pressure is related to the amount of circulating plasma proteins. Our observations show a linear correlation between the plasma volume and the circulating plasma protein in the normal and patient groups (Fig. 2). Madden and Whipple¹⁷ report that the plasma proteins are in dynamic equilibrium with the tissue proteins. This seems likely in our patient group, for the reduction in weight must have occurred at the expense of fat and protein. Negative nitrogen balances were observed in several cases on whom such studies were done. The metabolic status of these individuals is that of semi-starvation. It is of primary importance that proper attention be given to insure an adequate protein intake in these patients so that positive nitrogen equilibrium may be restored.

Although the patients with chronic

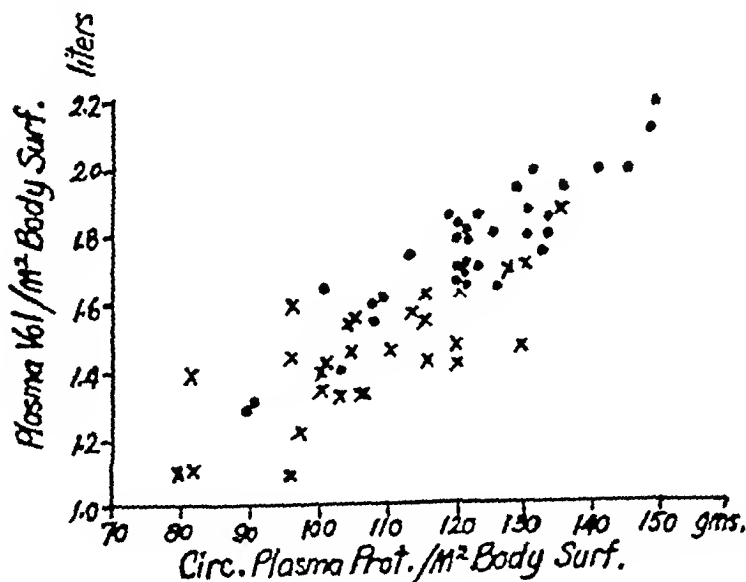


FIG. 2.—Plasma volume plotted against circulating plasma proteins per square meter normal body surface in the 27 wounded soldiers studied and in 34 normal male controls. The closed circles represent individual values in the normal control group. The crosses represent individual values in the patient group.

wound infections and pronounced weight loss studied by us showed a slightly elevated mean plasma protein concentration, their mean total circulating plasma protein was actually 12.8% less than the estimated mean normal value. Sole reliance on plasma protein levels as indices of the plasma volume, circulating plasma proteins, and nutritional status of such patients may therefore be quite misleading. Two of our patients had plasma protein values below 6.5 gm. per 100 cc., and 6 patients had levels of 8 gm. or more. Evidence of dehydration in the latter was absent. Available (thiocyanate) fluid volumes measured in 3 of these patients were normal. While data on the plasma protein fractions in our patients are incomplete, the elevated plasma protein values observed are, in all likelihood, the result of an elevated globulin fraction and concomitantly lowered albumin fraction as has been noted in chronic suppurative infections.^{2,4} It is highly probable that the reduction in plasma volume is largely the result of a lowered osmotic efficiency of the plasma secondary to a reduction in circulating plasma albumin.

The changes in the hematocrit in our 27 patients failed to indicate reliably the extent of change in the circulating red cell volume, for the average reduction in the latter was 2.7 times that shown by the former. Our observations are in agreement with those of Hopper *et al.*¹⁴ that the dye method indicates changes in the plasma volume more readily than changes in the serum protein concentration or hematocrit.

Similarly, changes in the hemoglobin concentration were poor indices of the degree of oligochromemia in our patients, for the mean reduction in their circulating hemoglobin was 2.6 times the average decrease in the hemoglobin concentration. The anemias in our cases of chronic wound infection were refractory to liver extract and iron therapy. This has been attributed to a disturbance in the intermediary metabolism of iron with a secondary failure to form heme.⁵ Our experience indicates

that until the associated infections are cured, the only effective treatment for the anemias observed in these patients is transfusions of whole blood in adequate quantities repeated as frequently as necessary. Many of our patients would not have survived were it not for repeated transfusions given while measures to control these infections were being instituted.

Unlike healthy individuals, patients with chronic wound infections, nutritional depletion, and a lowered blood volume cannot withstand relatively minor blood losses without being predisposed to shock, peripheral vascular collapse, and anoxic complications. These events have been observed in such patients following surgical procedures. This is not surprising in view of the lowered blood volume, red cell volume, and circulating hemoglobin observed in them, and the fact that the blood loss in ordinary surgical operations may be considerable.^{6,9} We concur with Lyons¹⁶ that the maintenance of an adequate blood volume is of utmost importance in the prevention of shock and its complications in these patients. The results of this study emphasize the necessity for whole blood transfusions in adequate quantities in the preoperative and postoperative management of such cases. Our experience is in agreement with that of Coller *et al.*,⁶ and Stewart and Rourke²⁸ that the quantity of blood loss is not reflected by changes in the hematocrit, hemoglobin, and plasma proteins prior to and immediately after an operation. Reliance on these determinations may lull the surgeon with a false sense of security when indeed shock may subsequently intervene. It is clear that in these patients the indication is adequate replacement with whole blood, for the administration of plasma neglects the desired augmentation of the circulating hemoglobin and serves to prolong and aggravate the existing anemia.

Of the 19 patients whose available (thiocyanate) volumes were measured, 8 (Cases A1, A3, A4, A5, A12, B17, B19, B20) (Table 3) showed volumes in excess

of 40% of the body weight noted at the time this study was made. The increased volumes observed in these cases are explained partly by the pronounced cellular wastage, fat loss, tissue destruction, and toxemia, and the replacement by interstitial fluid. In Cases A1, A4, B17 and B20, the available fluid volumes were respectively equivalent to 57, 51.7, 52.5, and 66.5% of the observed body weight. These figures denote exceedingly large increases which cannot be explained solely on the basis of increases in extracellular water. In Case B20, the value approximates that for total body water. By tissue analysis methods, Overman²¹ has established that under certain conditions which are not entirely understood, thiocyanate ion appears to enter the tissue cells as a result of generalized permeability alterations. This offers a likely explanation for the excessive increases in available (thiocyanate) fluid volume observed in Cases A1, A4, B17 and B20, all of whom were extremely ill, febrile, cachectic, and suffered with severe chronic wound infections. Of the latter, only Case A4 survived. Excess fluid in the serous cavities and tissues were absent at autopsy in Cases A1, B17 and B20. A second available (thiocyanate) fluid determination in Case A4 made 2 months after the first measurement and following marked improvement and a gain in weight of 3.5 kg., showed that the available (thiocyanate) fluid volume had decreased from a value equal to 51.7% of the body weight to a value which was 34% of the body weight. We associate this change with the recovery phase of tissue permeability alterations occurring in this patient. It is our experience that in such patients a markedly elevated available (thiocyanate) fluid volume approaching the value for total body water is associated with a grave prognosis.

Summary. 1. Body fluid data on 34 normal young adults and 27 patients with chronic wound infections, extensive weight loss, and anemia are reported.

2. The patients studied show an average reduction in blood volume of 1430 cc. (24.2%). This is the result of decreases in plasma and red cell volumes, the decrease in the latter being 1.8 times that shown by the former. Maintenance of an adequate blood volume to prevent shock and its complications is of utmost importance in these cases. For this purpose whole blood in adequate quantities, given repeatedly if necessary, is indicated preoperatively and postoperatively.

3. The mean reduction in the red cell volume and circulating hemoglobin observed in our patients was approximately 2.5 times that shown by the respective mean changes in the hematocrit and hemoglobin concentration. Blood volume determinations offer a practical and more reliable guide in therapy.

4. The available (thiocyanate) fluid volumes were in excess of 40% of body weight in 8 of 19 patients measured, and equal to more than 50% of the body weight in 4 cases. The values in the latter are attributed to the entrance of thiocyanate ion into the cells as a result of generalized permeability alterations following prolonged nutritional depletion, pyrexia, severe chronic polymicrobial infections, and toxemia. In 1 case the available (thiocyanate) fluid volume approached the generally accepted value for total body water.

5. Close correlation between the reduced plasma volumes and circulating plasma proteins were observed in our patients. In general, the plasma protein concentrations failed to reflect the degree of change in the total circulating plasma protein and plasma volume and may, in fact, fail to indicate the direction of change in these cases. As an index of the nutritional status, the plasma protein concentration may be quite misleading. Re-establishment of positive nitrogen equilibrium by an adequate protein intake is indicated in all these patients.

6. The clinical implications of these findings are discussed.

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RADIOLOGY

UNDER THE CHARGE OF

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ROENTGENOLOGIC EVIDENCE OF BILIARY REGURGITATION: ROENTGENOLOGIC CONTRIBUTIONS TO THE DIAGNOSIS OF HYPOPARATHYROIDISM, APPENDICITIS; MESENTERIC THROMBOSIS

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1. *Roentgenographic Demonstrations of the So-Called Regurgitation Phenomenon in Jaundice.* In a series of 460 cholangiographic examinations in which diodrast (3,5-diiodo-4-pyridone-N-acetic acid diethanolamine) was used, Rigler and Mixer¹⁰ observed 8 patients whose renal pelves were clearly outlined by the cholangiographic medium on roentgenograms made at intervals of from 5 to 30 minutes after the drug was injected into the common bile duct. Cholecystectomy had been performed on all of the patients and a drainage tube had been inserted into the biliary ducts. In all instances there was a partial or complete obstruction of the common bile duct at its ampullary extremity by a biliary calculus. In several of the cases in which more than one cholangiographic examination was performed, the renal pelves were filled with the contrast medium at one examination but not at another, although the biliary ducts were well distended at the time of each cholangiographic observation. This apparent inconsistency is believed to be due to a failure to exert sufficient pressure during injection to cause regurgitation from the biliary radicles into the blood stream.

In the opinion of Rigler and Mixer the phenomenon of regurgitation occurs more frequently than their par-

ticular series of instances indicates. The renal areas are often obscured on roentgenograms by gaseous and other intestinal residues, particularly those that are opaque to roentgen rays, and small concentrations of opaque liquids in the renal pelvis are easily overlooked. They pointed out that optimal conditions must prevail if the phenomenon is to be observed.

Three possible explanations were offered for this rapid entry of the cholangiographic medium into the blood stream and its excretion by the kidney in a concentration sufficiently high to make the renal pelvis visible on roentgenograms. Absorption from the intestine was not regarded as a plausible explanation because obstruction at the lower end of the common bile duct was demonstrated in all cases, and in no instance was an appreciable amount of the medium observed in the intestine. Direct absorption of the medium through the mucous membrane of the biliary ducts was thought to be improbable for several reasons. In the first place, evidence that the medium had entered the blood stream at all was elicited in but a small percentage of the cases in which a well-distended biliary duct system was demonstrated by cholangiography. If the mucosa of the biliary ducts were capable of ab-

sorbing significant amounts of the medium then every cholangiogram revealing a well-distended set of biliary ducts should also reveal the medium in the renal pelvis. In the second place, the medium was observed to enter the kidneys very rapidly, in one case as early as 5 minutes after it was injected. The experimental work of Shafiroff and Bierman¹¹ was cited in support of the proposition that absorption of the medium by the mucous membrane of the biliary ducts takes place slowly, if at all. They ligated the cystic duct of cats and carefully preserved the blood vessels and lymphatics of the gallbladder. They then injected various radio-paque substances into the lumen of the gallbladder. Crystalloid substances such as sodium iodide and most of the organic compounds of iodine commonly used in excretory urography, of which diodrast is an example, were absorbed from the lumen of the gallbladder only after 6 hours, and they appeared in the kidneys hours later. Rigler and Mixer pointed out that this represents absorption by the mucous membrane of the gallbladder and they thought it reasonable to assume that absorption by the mucous membrane of the biliary ducts would be even more markedly delayed. For these reasons they held that, at best, an insignificant amount of the cholangiographic medium was absorbed by the mucous membrane of the biliary ducts, and they concluded that the mode of entry of the medium into the blood stream in quantities sufficient to be roentgenographically demonstrable in the kidneys was directly into the hepatic sinusoids and veins and thence into the blood stream. Apparently the pressure under which the cholangiographic medium was injected in the cases in which this regurgitation occurred was too great for the walls of the biliary canaliculi to tolerate. The speed with which the medium gained access to the kidneys and the amount

of medium demonstrated there indicate that rupture of the canaliculi must have occurred. In his discussion, Rigler mentioned that the more familiar phenomenon of pyelovenous backflow observed not infrequently in retrograde pyelography is an analogous situation.

In addition to providing another and a very graphic link of evidence for the existence of a relatively easy retrograde communication between the biliary ducts and the blood stream, especially under conditions of elevated intraductal pressure, this observation of Rigler and Mixer offers a new and very plausible explanation for some of the unfavorable reactions which occasionally are associated with cholangiography. Allergic types of reactions like those observed sometimes, and still too frequently, when the organic compounds of iodine prepared especially for use in excretory urography are administered by the intravenous route, are observed rarely, if at all, after cholangiography. Rigler encountered none over a period of 6 years in which he used diodrast for this purpose, and he said that he was aware of no report of such a reaction in the literature. Rigler and Mixer said that mild or even severe febrile reactions were not uncommon after cholangiography in their experience. They intimated that a mild or transient bacteremia might be responsible for those reactions. Such reactions occur only in cases of infection of the biliary tract. They reasoned that if the cholangiographic medium can be regurgitated into the blood stream it is also possible to force the bacteria present in the biliary ducts into the blood stream. Experimental work on animals, unpublished as yet, which was done in their laboratory, supports this contention. They discredited the idea that simple distention of the biliary radicles might be a cause of these febrile reactions. In none of the cases in which they demonstrated regurgitation of the cho-

cholangiographic medium into the blood stream was there evidence of infection of the biliary tract, and in none of these cases was there evidence even of mild unfavorable reaction. In all of them however, the biliary ducts were well distended. Neither could they agree with authors who attribute the severe reactions to regurgitation of the medium and presumably other possibly infectious content of the biliary ducts into the pancreatic duct. Their collaborator, Bergh², found that the pancreatic duct received the contrast medium in about a third of a series of cholangiograms he studied. Since the incidence of unfavorable reactions after cholangiography is much lower than this, Rigler and Mixer contended that the entry of cholangiographic medium and, with it, other contents of the biliary ducts into the pancreatic duct is probably not responsible for the postcholangiographic difficulty.

Very appropriately, Rigler and Mixer issued the warning that great care should be exercised in performing the necessary maneuvers of cholangiography. Injection of the medium should be made at the lowest possible pressure to obtain moderate filling of the intrahepatic ducts. They suggested that the medium might best be injected under roentgenoscopic control to facilitate the use of the minimal amount of pressure and yet realize the full benefit of the diagnostic procedure. They also insisted on the use of all possible aseptic precautions in the preparation and administration of the cholangiographic medium.

2. *A roentgenologic cue to the diagnosis of spontaneous hypoparathyroidism.* Camp⁴ recently reported the results of some investigations he made on the significance of symmetrical calcification of the cerebral basal ganglia. He found 12 cases in which this phenomenon occurred and in which there was definite

clinical evidence of parathyroid insufficiency and tetany. In general, the patients' symptoms were those which commonly complicate hypoparathyroidism, cataracts, convulsions, mental retardation and trophic changes. Four of the patients were males; 8 were females. At the time of onset of symptoms, 7 of the patients were less than 10 years old, 3 were between 10 and 20 years of age, 1 was 39, 1 was 42. At the time of Camp's examination, however, 1 patient was 21½ years old, 4 were between 10 and 20 years of age, 3 were between their 20th and 30th years, 1 was 32 years of age, and 3 were more than 40 years old. In 11 of the cases the parathyroid insufficiency was spontaneous; the other patient underwent thyroidectomy at the age of 19 years and hypoparathyroidism followed subsequently.

The pathogenesis of the calcification is fairly well understood. Originally, a deposition of colloid takes place in and around the smaller cerebral arteries, especially in the media and adventitia. The veins are rarely affected. Later, the deposits of colloid become calcified and, as they coalesce, perivascular sheaths and concretions are formed. When the process is extensive the capillary vessels may be occluded, but the lumens of the arteries are rarely diminished. Changes like these are frequently observed at necropsy, especially in the globus pallidus and in the dentate nucleus of the cerebellum, and when they are of minor degree they are often thought to have little significance. The pathologic process described may become marked at any age, and in either sex and in response to many diseases, not all of which are associated with neurologic symptoms. Camp and those who worked with him on this project expressed the opinion that these changes have been most marked and, therefore, most subject to roentgenolo-

gic detection in cases of parathyroid deficiency and other diseases featured by mental deterioration, sometimes with and sometimes without convulsions or motor symptoms referable to the extrapyramidal system. They did not hold the calcification responsible for the mental deterioration and convulsive seizures, because adequate treatment of the parathyroid insufficiency improves the mental condition of the patients and stops the convulsions; but the cerebral and cerebellar calcification undergoes no roentgenologically demonstrable change.

The roentgenologic appearance of symmetrical calcification of the cerebral ganglia was described as a distinctive one, although the degree and extent of demonstrable calcification vary within wide limits corresponding presumably with the stage of the disease that is present at the time of roentgenologic examination. At the stage when the calcareous deposits are microscopically small, they are expected to escape detection on roentgenograms made during life. The earliest demonstrable deposits Camp observed were small, irregular and discrete, and they were distributed symmetrically in the regions of the several basal ganglia, especially in the putamen and the caudate nucleus. With more extensive calcification, especially when it occurred in the dentate nucleus of the cerebellum and in the folds of the cerebellar hemispheres, the shadows assumed a wavy linear appearance. With coalescence of calcareous masses the shadows were larger, denser and more obvious. Calcified deposits in the cerebellum and in the deeper layers of the cerebral cortex were observed to occur coincidentally. They sometimes were so marked as to simulate vascular lesions or calcified gliomas. Calcification limited to the basal ganglia of 1 side was observed in 2 cases and it was

minimal in both cases. Neither patient had evidence of neurologic or parathyroid disease.

The bilateral and symmetrical arrangement of the deposits was the feature which served to prevent diagnostic confusion with cerebral neoplasm. Pneumographic examinations were occasionally used to clarify doubtful situations. Deposits of calcium in the choroid plexus were confusing only in anteroposterior projections of the skull; lateral projections of the skull, however, readily revealed the characteristic, more anterior position of calcareous deposits of the larger basal ganglia.

Camp was careful to point out that calcification of the cerebral basal ganglia is not found exclusively in cases of parathyroid insufficiency. In the course of his study he observed the calcification in patients who had had encephalitis, tuberous sclerosis, toxoplasmosis or mental deficiency since birth, and in some who did not have any clinical signs and symptoms referable to the condition. The observation, in a relatively short period, of 11 instances in which parathyroid insufficiency and calcification of the basal ganglia were associated was to him more than mere coincidence. Since parathyroid insufficiency responds so promptly and so well to treatment, the diagnosis should be established as frequently and as quickly as possible. Camp expressed the belief that at least an occasional mentally retarded or handicapped patient might be salvaged if all patients with known or suspected parathyroid insufficiency were subjected to roentgenologic examination of the skull, and if estimates of the concentration of serum calcium were made in all cases of symmetrical calcification of the cerebral basal ganglia.

3. *Some roentgenologic contributions to the diagnosis of vermiform appendi-*

citis. If a roentgenologist is asked to make a diagnosis of appendicitis, he makes use of diagnostic criteria in no way different from those used by other physicians. He takes a detailed history, makes a careful physical examination of the patient, and gives due consideration to special examinations of the urine and blood. Naturally, he is more "x-ray conscious" than many another physician would be, and if his roentgenologic equipment happens to be handy he will probably want to submit the patient to certain very simple roentgenologic examinations, none of which are rigorous enough or time-consuming enough to have an unfavorable effect on the patient's prognosis. The preliminary procedure would probably be a so-called scout film (preliminary survey) of the abdomen, preferably in anteroposterior and postero-anterior projections. His principal concern in this examination is the exclusion of certain abdominal abnormalities which produce clinical manifestations that simulate those of appendicitis. Urinary lithiasis usually, and biliary lithiasis frequently, can be disclosed by this simple maneuver; the existence, site, and usually the nature and significance of other intra-abdominal calcified masses can be determined; opportunity is given to establish the presence and to consider the significance of abnormal intra-intestinal and extra-intestinal accumulations of gas. If, by chance, the cecum contains enough gas to make this organ identifiable as such, the roentgenologist may wish to perform roentgenoscopy to correlate the abdominal tenderness and muscular reaction with the cecum, and by inference with the appendix.

Not many roentgenologists today place much reliance on the evidence of appendicitis elicited by administering opaque suspensions by mouth or by enema in the hope of making the

lumen of the appendix visible on roentgenograms or on the roentgenoscopic screen. It is true that the exact intra-abdominal position of the vermiform appendix can be determined in this way; its mobility can be tested by manipulation and its anatomic relation to the cecum can be depicted. These determinations are possible, however, only if the appendix receives the contrast medium. This will be unlikely if the appendix is actually diseased in the clinical sense, although failure of the appendix to receive the contrast material is in no sense acceptable evidence of appendiceal disease. Nevertheless, to be able to demonstrate a precise correlation between significant abdominal tenderness and abnormal muscular reaction to palpation, and the tip of the cecum may, especially when the cecum is not in its usual position, be helpful in clarifying a dubious situation.

Even if there were distinctive roentgenologic signs of appendicitis, administration of opaque material by mouth would rarely be undertaken when the diagnostician is confronted with the possibility of acute appendicitis. Hours are consumed waiting for the material to reach the ileocecal region, and these are critical hours. Administration of opaque material by enema is much less time-consuming but it is not without danger when perforation is imminent, because it is a rigorous procedure, and no matter how deftly performed it excites the motility of the intestine at the very time when such excitement should be scrupulously avoided. In the interval between recurrent acute or sub-acute attacks of appendicitis, opaque material can probably be administered with relative safety by either route. But what is the diagnostic yield? Again it is true that lesions of the intestinal tract other than appendicitis, but perhaps simulating it in their clinical manifestations, will be detected in this way.

But aside from the apparently rare demonstration of an inspissated non-opaque fecal mass in the lumen of the appendix, or verifying the intraluminal or juxtacecal situation of an appendicolith impregnated with calcium, there are no reliable and distinctive signs of clinically significant appendicitis. The patient may complain of tenderness when the cecum or the appendix is manipulated during roentgenoscopy and there may be some voluntary or involuntary abdominal muscular reaction on the part of the patient to the palpation, but at most these are signs of doubtful value and but a minor part of the clinical syndrome. If the appendix fills with barium suspension, and there is reason to think that 3 out of 4 appendixes will do this either with the barium meal or with the barium enema, or with both, the roentgenologic examiner may get the impression from his manipulations during roentgenoscopy, or even less reliably from a set of serial roentgenograms of the ileocecal region, that the appendix is fixed unnaturally to the cecum or to the abdominal parietes, and he may interpret this to be a residuum of previous attacks of appendicitis. Unfortunately the natural fixations of the appendix are most difficult to distinguish from the unnatural ones, in fact, many examiners of recognized competence experience difficulty in establishing merely the fact of fixation. Other more or less significant changes that may be observed in the barium-filled appendix are: (1) its infracecal, paracecal or retrocecal position; (2) diverticula, which are very rarely encountered and of questionable clinical and pathologic significance; (3) kinks and tortuosity, potential factors in the pathogenesis of acute appendicitis when it can be established that they are genuine, and this is not easy to do; (4) appendiceal stasis, the significance of which is impossible to esti-

mate because it is known that apparently normal appendixes can retain roentgenologically demonstrable quantities of barium for days or weeks; (5) opaque foreign bodies, especially gunshot, which may be retained for prolonged periods; (6) small, nonopaque masses which may be small fecaliths or inspissated mucus, probably formed in situ, the significance of which is questionable; (7) peculiar and as yet unexplained changes in the relief pattern of the appendiceal mucous membrane.

Neoplasms of the vermiform appendix, malignant and benign, the incidence of which is exceedingly low, are occasionally made manifest not by producing demonstrable change in contour of the contrast-filled appendix, because the appendix is not expected to receive the contrast material when so affected, but by producing a compression or displacement type of deformity of the cecum or adjacent portion of aboral ileum. The tumefactive chronic peri-appendiceal abscess or granuloma produces a similar roentgenologically demonstrable change.

These remarks were prompted by the appearance in recent issues of radiologic journals^{5 6 7 12} of several articles pertinent to the subject of appendicitis. Three of these called attention again to the significance of calcified appendicoliths. To those readers who accept the theory which Wangenstein¹³ developed in a very convincing manner, namely, that obstruction of the appendiceal lumen is the fundamental factor in the pathogenesis of acute appendicitis and that the appendicolith is the most important single agency in the development of the obstruction, these discussions will have a special appeal. It is known, of course, that appendicoliths are frequently found in appendixes removed surgically for acute appendicitis (in 67% of a series of cases of acute appendicitis analyzed by Bow-

ers³), but the preoperative diagnosis has been made relatively seldom. The diagnosis is strictly a roentgenologic problem and it is a relatively simple one when the concretion is fairly large and when it is impregnated with enough calcium to make it opaque to the roentgen rays. The incidence of appendicoliths of this kind has been thought to be very low. Yet Felson and Bernhard⁷ encountered 10 instances in the course of 3 years during which time they estimated that 300 appendectomies were performed in the hospitals in which the 10 patients were seen. They also made an analysis of 100 cases reported in the literature since 1906 and of the 10 cases of their own. (See below.) Thomas¹² reported on the clinical histories and roentgenologic findings in 8 cases, 6 of which were observed since 1945 and 4 of them in that year. In Childe's⁵ series of 8 cases the patients were children 12 years old or younger who were observed in a period of 11 years in 1 hospital. These reports are not mutually inclusive. In only 11 of the 100 cases reviewed by Felson and Bernhard⁷ was the diagnosis made preoperatively and confirmed surgically. Summarizing the important conclusions which the authors of these papers independently concurred in making, these points can be made: (1) appendicoliths appear on roentgenograms of the abdominal field as oval or round or triangular or irregular opaque masses, which vary in size between 0.5 cm. in diameter to 3.0 by 1.5 cm. in length and width, and usually show evidence of lamination (94%, according to Felson and Bernhard), are situated in the far right lateral portion of the abdominal field at various vertical levels between the shadow of the lower border of the liver and that of the spine of the right ischium. (2) The shadows are large enough and opaque enough to be seen on the roentgeno-

gram of the abdomen, although special projections are sometimes necessary to identify the shadows as appendicoliths and occasionally it is necessary to perform urographic and cholecystographic examinations to exclude urinary or biliary calculi or to examine the ileocecal region with the opaque meal or the opaque enema to prove a close anatomic relationship of the shadow with the cecum. (3) In about two thirds of the cases reported there was but 1 appendicolith; there were 2 or more appendicoliths in a third of the cases. (4) Not all appendicoliths are hard and firm; according to Felson and Bernhard about a fourth of them have a soft consistency. (5) Since the coincidence of acute appendicitis with appendicolithiasis is very high, and since the incidence and imminence of perforation of the appendix at or near the appendicolith is also very high, surgical removal of the appendix should be attempted as soon as the diagnosis is made; Thomas was especially insistent on this point and made the apt comment that it is more important to remove an appendix containing stones than to remove a gallbladder with stones since rupture of the gallbladder is a comparatively unusual complication of cholecystic disease. (6) Roentgenographic examination of the abdomen should be performed routinely whenever the diagnosis of appendicitis is being entertained.

Euphrat⁶ reviewed the literature on mucocele of the appendix and reported a case in which, by using a well-defined roentgenologic syndrome elaborated by Akerlund¹, he was able to make the correct diagnosis prior to operation. The patient was a woman, aged 42 years, who for 10 months had had dull pain in the lower part of the right side of the abdomen while lying down. Physical examination revealed a smooth, round, slightly tender, very mobile mass at the level

of the anterior superior spine of the ilium. Roentgenologic examination of the colon showed the cecum to be displaced medially and anteriorly by a reniform, mobile, sharply circumscribed mass which measured about 6 by 10 cm. The mass maintained a close anatomic relationship to the cecum when manipulated, and it produced a concave deformity of the lateral and posterior borders of the ileocecal coil by its close contact. In the central portion of the mass there was an accumulation of calcareous material arranged in the shape of a swastika. No contrast material was observed to enter the lumen of the appendix. On the basis of these findings the diagnosis of mucocele of the appendix was made. The diagnosis was confirmed at operation. Qualitative tests of the contents of the mucocele were strongly positive for calcium but there was no trace of barium. This appears to be the fourth reported case of mucocele of the appendix in which the correct diagnosis was made before operation or necropsy. Euphrat expressed the opinion that in the past the diagnosis was usually missed because the presence of a mucocele was not considered. Undoubtedly there have been other instances, as yet unpublished, in which the diagnosis was made preoperatively and subsequently confirmed, for Akerlund's criteria are so definite and so readily elicited. The only feature of the syndrome distinctive for mucocele is the deposition of calcium in the substance of the tumor or in a plaque-like arrangement in its walls. Benign and malignant neoplasms of the appendix are manifested roentgenologically in a manner similar in all other respects. A well-localized chronic periappendiceal abscess may effect similar changes. Obviously the clinician and the roentgenologist should consider all the possibilities when alterations in the

ileocecal region of this general nature are encountered in practice.

4. *Roentgenologic aid in the diagnosis of mesenteric thrombosis.* Some years ago, Rendich and Harrington⁹ reported 3 cases of mesenteric thrombosis, in 2 of which they postulated a diagnosis of mesenteric thrombosis on the basis of observations made in the first case. In this case the patient was a woman, aged 75 years, who entered the hospital because of obstipation and abdominal pain of about 60 hours' duration. The clinical diagnosis was intestinal obstruction. Roentgenographic examination of the abdomen revealed distention of the small intestine and of the right half of the large intestine with gas. The column of gas in the large intestine ended abruptly at the transverse colon limb of the splenic flexure. This suggested mechanical obstruction; but, surprisingly, the opaque enema readily passed through the site of the suspected obstruction to fill the entire colon. The patient died the next day. Necropsy revealed thrombosis of the superior mesenteric artery; gangrene of the small intestine, cecum and part of the ascending colon, and hypertensive heart disease. In the course of the next nine months they observed two other patients who presented a similar intestinal distention on roentgenographic examination of the abdomen. On this basis alone they again offered the tentative diagnosis of mesenteric vascular occlusions. Both patients underwent operation. The diagnosis was verified, the gangrenous intestine was resected, and the patients recovered.

Recently Harrington⁸ reported 4 additional cases with precisely similar roentgenographic manifestations in which the diagnosis of mesenteric thrombosis was confirmed either at operation or at necropsy.

The authors^{8,9} did not say how often this diagnosis was made but disproved by subsequent events; therefore, they presumably did not have this experience. In any event, their published roentgenograms are convincing enough to make the clinician and roentgenologist give this diagnostic possibility due consideration whenever gaseous distention of the intestine abruptly terminating in the region of the splenic flex-

ure of the colon has occurred. It is the region which corresponds to the limit of the distribution of the superior mesenteric vessels. Obviously, it is another situation in which a simple roentgenologic procedure may offer an important clue to an obscure and relatively rarely encountered cause of genuine abdominal catastrophe, and one for which prompt decision might spell the difference between life and death.

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UNDER THE CHARGE OF

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PHARMACODYNAMIC CONSIDERATIONS OF ATROPINE AND RELATED COMPOUNDS

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FEW drugs have enjoyed such wide or varied use as atropine and its related compounds. Since some ancient time, when plants of the belladonna group were first ingested, up to the recent flood of synthetic modifications it has been a basic tool of witch doctor, physician and scientist. What basis does modern pharmacology give us for separating fact from myth—for replacing empirical hearsay with applied physiologic observations? Partial answers to these questions are given in the following review—an outgrowth of some investigations on methyl atropine nitrate at the University of Rochester.

CHEMICAL STRUCTURE AND BIOLOGIC ACTIVITY. What is known of the relationship between the chemical structure and biologic activities of these drugs? The active principle of the belladonna leaf and its extracts are a group of alkaloids, the most important of which is l-hyoscyamine. Atropine is a stereo-isomer of hyoscyamine and is optically racemic. The compound is the ester of tropine (an amino-alcohol) and tropic acid (alpha-phenyl, beta-hydroxy-propionic acid). Extensive investigations and modification of both portions of this molecule have been carried out to determine if possible which chemical and structural features are es-

sential for various biologic activities displayed by the parent alkaloid. Cushny¹⁸ (1920) felt that tropine itself was devoid of "typical" atropine action. However, its esters (tropeines) with a great variety of acids possess some degree of biologic activity. This was systematically studied by Dyson²² (1925). In general, he found that mydriatic activity was stronger in those compounds containing a benzene ring and/or an alcoholic hydroxyl group in the acidic portion of a molecule, but this was not the essential prerequisite it was often thought to be. For example alpha-hydroxy-beta-2 and pyridyl tropeine, which has no benzene ring portion, and ortho-hydroxy-benzoyl tropeine and meta-hydroxy-benzoyl tropeine which have no alcoholic hydroxyl groups, all possess mydriatic activity. Indeed the lactone itself possesses mydriatic activity as shown in terebthyl tropeine which has paralytic activity in addition; thus this property does not depend on a free hydroxyl group either. Opening the lactone ring destroys activity.

The irritant action of atropine is diminished with the substitution of halogen (chlorine or bromide) for the hydroxyl portion of the atropic acid residue.

Alkyl atropines are without activity.

Demethylation of the nitrogen atom results in decreased activity.

Methyl atropines have little or no central action but retain their peripheral activity.

It has been shown, then, that certain alterations in structure modify various types of atropine actions. Thus syntropan (the dimethyl-amino-propanol ester of tropic acid) is quite effective in reducing spasm of smooth muscle (though 20 times less effective than atropine itself in equivalent doses) it is almost without effect upon the central nervous system; it does not suppress pilocarpine, induces salivation, and is a very weak mydriatic.

Novatropine (methyl-homatropine hydrobromide) was shown by Quigley⁷⁹ (1937) to be somewhat less effective than atropine in inhibiting gastric hypermotility induced by insulin.

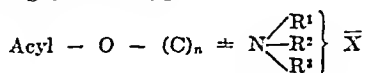
Homatropine is an excellent mydriatic, although somewhat transient in effect but has little systemic effectiveness, possibly because the body esterases are able to destroy it rapidly (Bernheim,⁶ 1942).

Eucatropine (4-mandelyloxy-1; 2; 2; 6-tetramethyl piperidine) has also been used clinically as a mydriatic.

Mydriasin is a trade name for methyl-atropine bromide.

Methyl-atropine nitrate is sold in this country under the trade names of eumydrine and metropine.

A long series of benzilic esters were investigated by Ing *et al.*⁵⁰ (1945) and they briefly reviewed the problem. Their observations covered compounds of the following general type:



which structurally are all alkamine esters where the (C)_n group is either a polymethylene chain or a cyclic structure. It is a striking fact that compounds of this general type have a peculiar affinity for neural structures and exhibit 1 or more of 4 kinds of pharmacologic actions, namely, cholinergic, atropine-like, curare-

like and local anesthetic, depending on the nature of the acyl radical and of the basic group. The discussion of these writers is worth quoting: "Cholinergic properties appear to be rather strictly confined to molecules containing 3 methyl groups on the N-atom and an aliphatic acyl radical (acetyl, pyruvyl, carbamyl, etc.); the (C)_n group is usually (CH₂)₂ but *n* may be 3 or the chain branched, *e. g.*, acetyl-methylcholine."

"Atropine and curare both antagonize acetylcholine drugs but the anatomic distribution of their effects is different. Curare-like properties are widely shared by alkamine esters, provided that the basic group is quaternary, but they may appear in a milder and more transient form in tertiary bases. The curare type of activity is characteristic of the onium cation and when it is displayed by tertiary bases most probably depends upon

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a relatively stable tertiary cation R₃NH⁺, because strong bases show it more markedly than weak bases.

"The results, which are reported in this paper, suggest that atropine-like properties ought also to be attributed to the cation and not to the free base. Conversion of a tertiary base into its metho-salt stabilizes the cation. Whereas tertiary

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cations R₃NH⁺ exist in equilibrium with the

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free base, thus: R₃NH⁺ + OH⁻ = R₃N + H₂O, quaternary cations are incapable of such a reversible reaction. We have found that such stabilization normally increases the atropine-like properties of tertiary bases. The attribution of atropine-like properties to the cation of the tertiary base not only explains our results but also brings the atropine-like action into line with the curare-like action; both are due to antagonism of an onium cation, acetylcholine, in cells adapted to respond to the latter, and our view is that the cationic nature of the antagonist, whether atropine-like or curare-like, is fundamen-

tally important. The conversion of a tertiary base with atropine-like properties into its metho-salt not only increases its activity in this respect, but also confers upon it strong curare-like properties, as Brown and Frazer¹⁰ (1869) discovered for atropine itself. The other structural features which lead to atropine-like properties in alkamine esters are more restricted than those which confer curare-like properties."

PHYSIOLOGIC ACTIVITY OF ATROPINE. In the previous section, while considering chemical structure, the term "typical" atropine activity was glibly used. Just what is typical atropine activity?

The most prominent physiologic action of atropine may be expressed as antivagal, that is, it tends to block the effects of acetyl choline on smooth muscle and gland cells, leaving adrenergic action dominant and unopposed. That atropine often selectively blocks the muscarinic action of acetyl choline without affecting the nicotinic effects of acetyl choline is illustrated by Frey's²⁹ experiment (1928) on the intestinal tract of the tench. Clark^{12a} (1937), however, offers well documented evidence to show that this is a generalization, and every tissue seems to be a law unto itself. For example, in *Helix pomatia* the heart action is inhibited by acetylcholine or muscarine. The presence or absence of atropine has no effect on this action. One becomes accustomed to thinking of atropine as a parasympatheticolytic drug with solely peripheral action, but these drugs have definite central nervous system and sympathetic components in their action. It is worth recognizing that although little is known about the exact way in which atropine works, there is abundant evidence that in no instance does it prevent nerve impulses from releasing acetylcholine but merely prevents effector cell response at some point peripheral to the nerve ending.

ACTION OF THE ATROPINE GROUP ON THE CENTRAL NERVOUS SYSTEM. Although the autonomic nervous system is

customarily thought of in terms of peripheral effects there is much evidence to show that the concept of levels of function applies to this system as well as to the motor division. In isolated organs effects can be produced by local application of specific autonomic drugs. Similar effects can be produced in intact animals, but segmental autonomic reflexes are well known and medullary centers are essential for regulation of the blood pressure. Heat regulation, primarily an autonomic function, is integrated at the level of the hypothalamus. Indeed, injection of acetylcholine (pituirine, or pilocarpine; adrenalin produces no effect) directly into hypothalamus results in massive parasympathetic discharges which can be blocked immediately by intraventricular injections of atropine (Henderson and Wilson,⁴⁷ 1936; Cushing,¹⁶ 1932). Other more complex integrations take place at the striatal level. Cortical areas governing autonomic function are found, generally corresponding in localization to those areas influencing corresponding somatic motor functions. For example, lacrimation occurs from stimulating eye-fields; salivation on stimulating motor representation of the face and tongue. The exact anatomic or chemical pathways through which these effects are mediated are not known. Heart rate, intestinal motility, sweating, conditional reflex salivation and psychic phase of gastric secretion are all known to be influenced by autonomic stimuli and also by cortical stimulation. The relationship that acetylcholine, and consequently atropine, might have in these central nervous system functions is not well understood at the present time.

Atropine stimulates the medulla and higher cerebral centers. It is believed that the drug acts by direct irritant action and not by removal of inhibition. Many people believe that this action on the central nervous system is the basis of the extreme toxicity of atropine in human beings as compared with other animals, notably rodents. Macht⁶⁵ (1923) studied

the effect of different doses of atropine on the reactions of albino rats in a circular maze. He found that very small doses would affect ability in this situation, 0.025 mg. stimulating and 0.05 mg. depressing their activity. The depressant dose of tropine was 5 mg., while tropic acid had no effect even in large doses. These results were obtained with rats: animals in which the lethal dose of atropine is relatively high and in which central nervous system effects are not prominent. On the other hand, psychic symptoms are among the most prominent signs of atropine intoxication in man leading to many grotesque and unusual actions. The intra-arterially injected acetylcholine causes a discharge from the central nervous system of a decerebrate cat resulting in an increase in tone of the innervated quadriceps. This action is blocked by atropine (Calma and Wright,¹² 1944).

Methylatropine possibly by virtue of its methylated structure (Dyson,²³ 1928) has equivalent peripheral action but little or none of atropine's prominent central action. Mice are killed by respiratory paralysis without any evidence of convulsant action (Graham and Lazarus,³⁸ 1940). Nyman reports that Brown and Frazer¹⁰ (1869) found that the stimulating effect of methylatropine (iodides and sulfates) had considerably less central action than equivalent doses of atropine. Erbe²⁷ (1903), in extensive clinical trials, failed to find evidences of central stimulation with therapeutic doses in man equivalent to those which had an action, when tested in a cat's eye, as great as that of atropine. Issekutz⁵¹ (1917) found that methylnitrates of both homatropine and atropine has stronger anticholinergic effects than the parent drugs and showed a marked curare effect but that the central effect was 30 to 50 times weaker. Solis-Cohen and Githens⁸³ (1928) state that ingestion of 60 mg. of methylatropine nitrate by a man caused weakness, particularly of the legs, but no cerebral symptoms. Monrad⁷¹ (1928) reports,

however, nystagmus, restlessness and convulsions as among the toxic reactions to methyl-atropine nitrate in his series.

Various belladonna derivatives have been used clinically for many years in paralysis agitans, athetosis and rigidity due to involvement of the extrapyramidal system and the basal ganglia. In general, little is understood as to their mechanism of action. Atropine is used for Parkinsonian symptoms, but the prominent side effects are often produced before alleviation. Highest recorded daily dose of atropine in this condition is 54 mg. (Hall,⁴⁰ 1937). No published results concerning methylatropine therapy in Parkinsonism were found.

Neither atropine nor methylatropine shows any regular action on the spinal cord.

Therapeutically this means that methylatropine has less prominent psychic side actions, while maintaining a peripheral effect in equivalent doses.

ACTION OF THE ATROPINE GROUP ON THE EYE. Atropine causes paralysis of the sphincter muscle of the iris which dilates the pupil (mydriasis). It also paralyzes the ciliary muscle of the lens leading to paralysis of accommodation (cycloplegia) and photophobia. The iris no longer responds to light and fails to react with convergence of the eyes. The parasympathetic fibers from the tectal outflow reach the eye *via* the third nerve and the ciliary ganglion and innervate the constrictor pupillae and the ciliary muscle, and form the efferent limbs of the light and accommodation reflexes. This reaction takes place by blocking the cholinergic nerve impulses and the action of acetylcholine. Intraocular pressure remains essentially unchanged, unless it is already elevated as in glaucoma, when it is increased further with atropine. There is some debate as to the mode of action of atropine in increasing ocular pressure in such circumstances. It is probable that lymphatic drainage is still more seriously interfered with by the action of atropine

on the ciliary muscle, blocking free flow between the 2 chambers of the eye.

Methylatropine was introduced clinically for mydriatic use by Lindenmeyer⁵⁹ (1903) and Goldberg³⁶ (1903). Their studies indicated that methylatropine produced maximal mydriasis in 30 to 75 minutes with final recovery in 40 to 72 hours. It produced maximal cycloplegia in 2 to 14 hours with recovery in 37 hours. These results may be compared with the recent results of Wolf and Hodge¹⁰³ (1946), who tested the effect of methylatropine and comparable solutions of homatropine and atropine in the human eye. Instilled in equal amounts into human eyes, homatropine had less mydriatic and cycloplegic effect than either of the other 2 drugs, and recovery from its effects was the most rapid.

Methylatropine nitrate had significantly less mydriatic action than atropine. The cycloplegic action was about the same as that of atropine.

Ing, Dawcs and Wajada⁵⁰ (1945) report that mydriatic activity of methylatropine was 2.88 times as strong as atropine when given intraperitoneally to mice but only half to equally as active with local application to the cat's eye. They felt that activity of these alkaloids depends on the method of administration.

ACTION OF THE ATROPINE GROUP ON THE RESPIRATORY TRACT. Atropine inhibits secretions of the nose, pharynx and bronchi, with resultant drying of mucous membrane. According to Henderson⁴⁵ (1923) 0.2 mg. causes decrease in nasal secretion without drying of the mouth in a 65 kg. man.

Elftman²⁵ (1943) describes autonomic innervation of bronchial smooth muscle. Parasympathetic fibers are vagal, reach the bronchial tree from anterior and posterior pulmonary plexi and exert a tonic constrictor action; vagal section is followed by bronchodilatation. Stimulation of the peripheral end of a cut vagus produces ipsilateral and contralateral constriction. In animals, constriction *via* vagus

may be reflexly invoked by irritating the mucous membrane of the upper respiratory tract.

Atropine also inhibits the smooth muscle of the bronchi and bronchioles, causing relaxation (Trendelenburg,⁸⁸ 1912; Sollmann and Gilbert,^{84a} 1937). These actions form the basis of a therapeutic use in asthma and catarrhal conditions and of its use preoperatively with morphine when anesthesia is given.

No specific references to the actions of methylatropine on the respiratory system were discovered, but on the basis of the similarity of its other peripheral actions to those of atropine, it probably has a similar effect on the respiratory system. Usener⁹² (1926) used dosages of 0.5 to 0.75 mg. of methylatropine nitrate for asthmatics.

ACTION OF THE ATROPINE GROUP ON THE HEART. Ever since the Webers⁹⁷ (1845) showed the inhibitory action of the vagus on the heart, there has been physiologic debate as to the exact rôle that the vagus nerve plays in controlling the activities of the heart. Hence there has been a similar confusion over the exact rôle of atropine; the essential action on the heart is antivagal, despite some claims for direct action of heart muscle. It is now generally believed that atropine alters the cardiac rate by stimulating medullary vagal centers in small doses of between 0.5 and 1 mg. (Heinckamp,⁴⁴ 1922; Gremels,³⁹ 1936). Recently accelerator fibers have been described in the vagus nerve of a dog (Kabat,⁵⁵ 1939) which may explain the initial slowing action of atropine. Atropine causes acceleration by blocking the vagal effect on the sino-auricular pacemaker in doses over 2 mg. (Crawford,¹⁴ 1923; Marris,⁶⁷ 1916). These effects are most prominent in young adults who have a strong vagal element. White⁹³ (1940) reports that the bradycardia resulting from stimulating the hypothalamus in humans was abolished by atropine. He also obtained acceleration from stimulating the posterior portion of the hypo-

thalamus. Atropine is sometimes used in Adams-Stokes syndrome to prevent vagal arrest. It will prevent the bradycardia caused by giving acetylcholine. Atropine is occasionally effective in heart block (Gilchrist,³⁵ 1933).

Issekutz⁵¹ (1917) found that methylatropine acts about 8 times as strongly as atropine in depressing the vagus of the frog. Nyman's⁷⁵ (1942) results (Tables 1, 2 and 3) working with atropine and other anticholinergic substances, demonstrate clearly that their effect on blood pressure, pulse rate and minute volume of the heart is most prominent in individuals with a strong vagal component. Atropine counteracts the peripheral vasodilatation and drop in blood pressure caused by acetyl-

choline and mecholyl. In toxic concentrations, however, it causes a drop in blood pressure because of central vasomotor depression. Despite its general effect of counteracting the vasodilatation, as previously mentioned, in certain cutaneous blush areas it causes vasodilatation perhaps by direct vascular effect. Methylatropine has been shown to influence the action exerted by adrenalin on the blood-vessels and has the power to cause paresis and ultimately complete paralysis of sympathetic motor termination in the vessels (Bergengren,⁴ 1925). Graham and Lazarus³⁸ (1940) found that in rabbits 0.05 mg. per kg. of methylatropine nitrate inhibited the bowel without affecting blood-pressure; however, 6 μ g. of atropine

TABLE 1.—THE EFFECT OF ATROPINE AND EUMYDRIN ON PULSE RATE

Subject	Drug	Dose (mg.)	Dose μ gn. 10 kg. \approx	Resting pulse	Maximum increase (%)
N, male	Atropine	0.84	100	50	20
	Methylatropine	0.84	100	52	73
O, male	Atropine	0.72	100	58	28
	Methylatropine	0.72	100	55	73
H, female	Atropine	0.65	100	85	21
	Methylatropine	0.65	100	84	46
P, female	Atropine	1.20	200	43	114
	Methylatropine	0.60	100	43	175

TABLE 2.—THE EFFECT OF ATROPINE AND EUMYDRIN ON THE OXYGEN CONSUMPTION, BLOOD PRESSURE, PULSE RATE AND MINUTE VOLUME OF THE HEART IN HUMAN BEINGS

Substance	Dose (mg. per kg.)	O ₂ per ml. per min.	Pulse rate	Blood pressure	Min. vol. of heart (liters)
Atropine	0.02				
(before injection)	..	239	54	129/90	3.4
30-40 min.	..	242	84	136/96	4.0
60-70 min.	..	246	78	140/98	maximum increase (18%)
Eumydrin	0.02				
(before injection)	..	236	54	122/83	3.2
30-40 min.	..	236	85	137/92	3.7
60-70 min.	..	222	98	143/93	5.7
					maximum increase (78%)

TABLE 3.—CHANGES IN SKIN TEMPERATURE RECORDED WITH THERMOCOUPLE AFTER EUMYDRIN

Location	Temperature before injection		Temperature after injection	
	30 min.	20 min.	20 min.	30 min.
	(0.1 mg. eumydrin/10 kg. body weight)			
Forehead	34.8°C	35.1°C	36.3°C	36.3°C
Right cheek . . .	34.2	34.3	36.8	36.0
Left cheek	33.9	34.0	36.7	35.8

0.2 mg. atropine caused responses of approximately the same magnitude when measured in the arms and hands.

abolished the effect on the blood-pressure of 0.15 μ g. of acetylcholine for an average 9 minutes. Six μ g. of methylatropine nitrate abolished the effect of 0.15 μ g. of acetylcholine for over 19 minutes. They were impressed with the more lasting effect of methylatropine in depressing cardiovascular autonomic cholinergic fibers.

It will be seen here, likewise in man, that methylatropine nitrate has a more marked effect on the blood-pressure and minute volume of the heart than equivalent doses of atropine.

ACTION OF THE ATROPINE GROUP ON THE SALIVARY GLANDS. It has long been known that the atropine alkaloids decrease salivary secretion. This antisialogogic action is made use of in routine preoperative medication. Hedenheim⁴² (1872) demonstrated that stimulation of chorda tympani after atropine no longer produced secretion of saliva from the sublingual gland. Langley⁵⁶ (1890) demonstrated that stimulation of the nerves leading to the parotid gland also did not produce salivation after atropine. Ewing²⁸ (1911) demonstrated that atropine decreased the quantity and composition of saliva. In greater doses, first the solids and then the amylolytic power of the saliva were reduced and that in the reverse direction normal amylolytic power returned first. It has been adequately demonstrated that whatever controls the secretory function, the effects produced are independent of those related to blood flow through the gland. The ability of these alkaloids to inhibit salivary secretion induced by pilocarpine has long been used as a method of testing the relative potencies. Isschutz⁵¹ (1917) who used 20 mg. of pilocarpine in rabbits found that 0.5 mg. of methylatropine was as effective as 1.5 to 2.0 mg. of atropine, thus making the quaternary base 3 to 4 times stronger than the parent alkaloid. Cushny¹⁸ (1920) found that methylatropine (bromide) was 1½ times as strong as atropine in antagonizing pilocarpine in-

duced salivation in dogs. Drugs were calculated as base. The dogs had fistulas in the submaxillary ducts, a standard technique of Cushny's, fully described in the literature. He used methylatropine bromide with a melting-point of 222° C. One-tenth mg. of atropine sulfate was weaker than 0.1 mg. of methylatropine but stronger than 0.05 mg.

Bulbring and Dawes¹¹ (1945) found that methylatropine was more effective than atropine in antagonizing pilocarpine-induced secretion in dogs. Giving atropine an arbitrary value of 100, the lowest value obtained for methylatropine nitrate was 133, the highest was 250, the mean 190±21. Nyman, in his extensive review of the atropine group, tested the effect of various drugs on pilocarpine-induced secretion in man. He found that in 7 consecutive control experiments on a male subject, O, an average secretion of 28.6±0.45 gm. of saliva in the 1st hour followed injection of 0.1 mg. of pilocarpine per 10 kg. body weight. Similar results were obtained in other individuals: 23.15 gm.; 24.8±0.57 gm.; 33.7±0.81 gm.; 30.65 gm. If subject O was given 0.05 mg. methylatropine nitrate (7 mg. per 10 kg. body weight) secretion was reduced to 14.95 and 15.55, in 2 different trials.

The following amounts of atropine sulfate antagonized pilocarpine-induced secretion (1 mg. pilocarpine per 10 kg. body weight). In subject O, whose unantagonized average secretion (given above) was 28.6 with 0.1 mg. (14 μ g.) the secretion was reduced to 14.35. Dose of 0.2 (28 μ g.) allowed secretion of only 9.7. Dose of 0.45 (63 μ g.) allowed secretions of 1.95 and 1.3 gm. in 2 different trials. Dose of 0.5 (70 μ g.) allowed secretion of 0.55. A dose of 0.6 mg. (84 μ g.) completely stopped secretion. Results with methylatropine nitrate in the same individual were as follows: dose of 0.07 (10 μ g.) allowed secretion of 12.15; dose of 0.1 (17 μ g.) reduced secretion to 5.25 (35 μ g.) inhibited secretion completely.

Note that this dose is only one-third the dose of atropine required to obtain the same antisialogogue effect. Similar results were obtained with 4 other individuals. Nyman charted and compared the activity of 14 other alkaloids with that of atropine in this regard.

ACTION OF THE ATROPINE GROUP ON THE ESOPHAGUS. Little information was discovered relating to the pharmacologic basis of the use of the atropine series in cases of cardiospasm. However, as early as 1881 Szpilman and Luchsinger⁸⁶ showed that the spasm produced by vagal stimulation resulting in contraction of smooth muscle in the lower third of the esophagus was depressed by atropine. The striated muscle of the esophagus apparently is not under autonomic regulation and, therefore, not affected by atropine. With the recent establishment of vagotomy as a frequent operation in duodenal ulcer patients, it is probable that more information relative to vagal control of the esophagus in man will be obtained.

Others believe that cardiospasm, pylorospasm and megacolon are results of sympathetic not parasympathetic denervation and arise from the inability to relax rather than from spasm of the sphincters. It must be reiterated, however, that response of the entire gastro-intestinal tract to autonomic stimulants depends on the physiologic state of the organs and the organism, and that general conclusions as to the reactions are dangerous.

ACTION OF THE ATROPINE GROUP ON THE STOMACH. The work of Bastedo³ (1936) and his article on the value of atropine and belladonna in stomach disorders with its accompanying references summarize this problem as of 1936. Here, too, much additional information will be gained on the vagal effects controlling the stomach from vagotomies. It has been thought since 1896 with the work of Ushakoff²¹ that very large doses of atropine in animals will lessen gastric secretion and lower the acidity. After vagus

and splanchnic nerves have been severed, the stomach continues to function, frequently with little if any dilatation; therefore its tone and rhythmic motility must be intrinsic, and the extrinsic nerves may be only regulatory, thus giving a more delicate control. The vagi and splanchnic nerves are for the most part not motor antagonists. The general effect of vagal stimulation is tonic while that of splanchnic stimulation is tonic to the pylorus and relaxing to the stomach wall. But stimulation of either may result in increased tone when the stomach is hypotonic, and in decreased tone when the stomach is hypertonic. Because these nerves are not a balanced mechanism in control of the gastrointestinal tract, abolition of one does not necessarily result in overactivity of the antagonist. Atropine may act on all nervous structures but its most regular action is to render vagal stimuli ineffective.

The effect of atropine on gastric secretion is best considered in relationship to the various phases of activity. Secretion occurring in the psychic phase was abolished by atropine in animals. Doses of $\frac{1}{16}$ grain reduce the amount of secretion in the psychic phase but does not abolish it in humans. It is quite possible that this physiologic atropine reaction is the basis of decreased appetite in humans following atropine. There is some evidence that the intestinal phase of gastric secretion is partly mediated through the vagus in animals and that this effect may be abolished by atropine (Ivy,⁸² 1935). The effect of atropine on the chemical phase of gastric secretion has been the subject of much debate. Bastedo³ believes that there is some reduction in free and total acid with section of the vagi, and with doses of atropine the equivalent of 2 grains for humans, cats show a decrease in secretion as well as in acid and mucin content, but the secretion is not completely abolished. Generally, patients tend to show a decrease in the volume of

secretion following atropine, without a corresponding decrease in acid. After a dose of 2 mg. of atropine sulfate (sufficient to produce dryness of the mouth, blurred vision, tachycardia and cerebral symptoms), the total volume was reduced, but a test breakfast of alcohol produced a normal amount of secretion. Large doses of atropine depressed the mucin content before affecting the acid content, a dangerous effect from a standpoint of ulcer patients in whom mucin has been shown to protect against irritation by acid.

In summary, the enormous doses of atropine possible in experimental animals may reduce and even abolish the secretion of gastric juice. In man the maximal therapeutic dose tends to reduce the psychic phase and possibly the intestinal phase of gastric secretion and thereby reduces the total secretion. It also tends to reduce the continuous interdigestive secretion for periods of 2 to 3 hours. In the chemical phase, doses large enough to cause toxic reaction may bring about a distinct reduction in the amount of secretion, though this is by no means a constant effect, and when present is short lived. If atropine is to be used in this manner, the minimal dose having any effect on the stomach is 1 mg. subcutaneously. Bastedo considers any smaller doses merely homeopathic.

Nyman studied this problem and was unable to show that methylatropine was any more effective than atropine in this regard.

THE EFFECT OF THE ATROPINE GROUP ON THE PYLORUS. Schroeder⁵¹ (1933) believes that the normal innervation of the pyloric sphincter is tonic, rhythmic relaxation following the beginning of the antrum contraction. Stimulation by adrenalin inhibits antrum peristalsis and the rhythmic activity of the sphincter, but increases the rate of flow. Pilocarpine has the reverse effect. Atropine acts like adrenalin. Ephedrine as well as the vaso-pressor and oxytocic principles of the

posterior pituitary lobe inhibit contraction. Morphine causes increased antrum peristalsis and contraction of the sphincter. Papaverine is more effective than atropine or posterior pituitary in antagonizing this morphine effect. Bastedo³ (1936) believes that pylorospasm may be either splanchnic-vagal or psychic in origin, and that atropine is only effective in those due to increased vagal tone.

Treatment of Hypertrophic Pyloric Stenosis. These properties have been employed in the treatment of pylorospasm and infantile pyloric stenosis. White¹⁰¹ (1923) developed the concept that some of these infants have a fundamental autonomic unbalance which atropine and methylatropine may be used to correct. Others speak of these infants as being hypertonic.

EFFECTS OF THE ATROPINE GROUP ON THE SMALL INTESTINE. Autonomic control of the small intestine is essentially regulatory, and the intrinsic nerve networks are of much greater importance in the usual physiologic state. Consequently there has been much confusion in the literature of the exact rôle played by atropine. Henderson and Roepke⁴⁶ (1937) feel that much of this arises from the undue weight given to the work of Magnus⁶⁶ (1908), who claimed that atropine stimulated the bowel. Examination of his experimental techniques revealed that his results are based on experiments with intestinal strips using concentrations of 1:4000 in a medium which we now would regard as highly unphysiologic. They point to the work of Unger⁶⁹ (1907) who showed that atropine produced a decrease in tone and movements in a concentration of 1:2,000,000 and less. Comparison with doses long believed effective in man (1 to 2 mg.) demonstrates that these doses probably lead to concentrations of 1:70,000,000 if the atropine is distributed throughout the whole 60 kg. of body weight, or 1:5,000,000 if the atropine is distributed only in the blood. Toxic

doses for man range around 10 mg. Even here the concentration will be in the range of 1:1,500,000. Thus the use of a 1:4000 solution seems fantastic when attempting to describe the effects of therapeutic doses.

In human beings an excellent study by Elsom and Drossner²⁶ (1939) tended to confirm the opinions long held by clinicians. In the normal duodenum, intestinal tone is high and motor activity great. There are 2 types of waves: (a) large peristaltic waves occurring every 1 to 2 minutes and lasting approximately 1 minute; (b) superimposed on these are frequent small undulations produced by rhythmical contraction. Administration of $\frac{1}{150}$ grain of atropine was followed in 10 to 15 minutes by a gradual fall in intraduodenal tone. The large peristaltic contractions were altered simultaneously, often becoming more pronounced as the tone decreased, then gradually diminishing in size and frequency and eventually disappearing. The small rhythmical waves decreased in size, though not in frequency. The effect was fully developed at the end of 20 minutes and lasted for 1 to 2 hours, after which there was gradual recovery.

The normal action of the jejunum and ileum consisted of small rhythmic undulations which were definitely decreased in tone and character following atropine. These results were obtained by means of a balloon inserted within the lumen of the gut of several human subjects. These results agree with those reported by Herrin⁴⁸ (1936) and White¹⁰¹ (1923) who maintain that gastro-enterospasm was a manifestation of autonomic unbalance in early infancy and was corrected by administration of atropine.

There have been no experimental studies of the response of the gut in human beings using methylatropine other than those discussed in connection with pyloric stenosis. However, Handovskii⁴¹ (1929) tested the effect of methylatropine nitrate, atropine and papaverine on isolated strips

of mouse intestine. He found that approximately 2 cc. of 0.2% solution of methylatropine hydrochloride would inhibit contraction, whereas approximately 6 cc. of 0.33% solution of atropine sulfate was required to accomplish the same effect; $2\frac{1}{2}$ cc. of papaverine hydrochloride (0.33% solution) would also inhibit contraction. However, papaverine and methyl-atropine nitrate seem to have synergistic actions, so that only 0.8 cc. of an equal mixture of 0.43% papaverine hydrochloride and 0.007% solution of methyl atropine hydrochloride were necessary to inhibit contraction. Graham and Lazarus³⁸ (1940) found that the spasmolytic powers of atropine and methyl-atropine nitrate were comparable; both drugs produced reduction in tone and loss of segmental movements of the intestine of rabbits anesthetized with ether. Both drugs antagonize the neurogenic spasm induced by eserine. The minimal effective concentration of both for rabbit jejunum was 1 part in 10,000,000. There is a definite inhibition for 2 or 3 minutes with dilutions of 1:5,000,000. Both drugs were without effect on spasm produced by barium chloride which is a myogenic stimulant. The range of sensitivity of rabbit intestine to these drugs was the same and depressed upper jejunum, duodenum, ileum and colon in that order.

THE EFFECT OF THE ATROPINE GROUP ON THE COLON. Doses of atropine between 0.4 and 0.6 mg. decreased the tone and activity of the colon for $1\frac{1}{2}$ to 2 hours, with gradual return to normal (Elsom and Drossner,²⁶ 1939). Jackmann and Barger⁵⁴ (1938) stated that doses of 0.0006 gm. produced definite depressing effects on colonic activity but had marked side effects which made it undesirable for routine clinical use.

Schroeder⁸¹ (1933) studied the effects of various drugs on the ileocecal valve and ileum. He believed that normally the sphincter undergoes tonic rhythmic relaxation following the beginning of ileal

peristalsis. Adrenalin inhibits peristalsis of the ileum and rhythmic activity of the valve but increases the rate of flow. Pilocarpine has the reverse effect. Atropine acts in the same manner as adrenalin.

OTHER EFFECTS OF THE ATROPINE GROUP ON SMOOTH MUSCLE. *Urter.* Atropine has an antispasmodic action on the ureter when it is in spasm and will decrease the increased tone resulting from morphine in man (Macht,⁶² 1918). No reports were found dealing with the effect of methylatropine on the ureter.

Biliary Duct and Gall Bladder. The atropine group exerts a mild antispasmodic action and strong enough to counteract contractions induced by morphine. Both nitrites and xanthins were effective against morphine contractions (Lieb and McWhorten,⁶⁷ 1915; Macht,⁶¹ 1917).

Uterus. Actions of the atropine group are of little demonstrable effect on uterine contractions, despite its wide use clinically in dysmenorrhea (Novak,⁷⁴ 1915). They are, however, able to counteract such effects as are produced by acetylcholine and its derivatives.

Urinary Bladder. The atropine group has a depressive effect on the detrusor muscle, especially when it is hypertonic (Edmunds and Roth,^{23a} 1920). MacCallum^{60a} (1906) reported that atropine had little effect on urine flow in rabbits but antagonized the depressant effect of pilocarpine. (See also Featherstone, R. M., and White, N. G., *J. Pharm. and Exp. Ther.*, 84, 105, 1945.)

The Effect on Sweat Glands. What long seemed a paradoxical action of the atropine group in inhibiting sweating (glands known to be supplied by sympathetic nerves) was cleared up with the discovery by Dale and Feldberg that acetylcholine was released by these nerve-endings, notwithstanding their anatomic relationships. Howe studied the effect of atropine in inhibiting sweating and found that atropine was capable of reducing the weight loss of infants due to insensible perspira-

tion 22%, as measured with a Sauter balance. Methylatropine is believed to have equivalent effect.

Effect on the Body Temperature. Even small doses of atropine frequently produce fever without other evidence of toxicity. White¹⁰⁰ (1929) studied this phenomenon and stated that at least 10% of the infants would develop fever of 38° or more when given therapeutic doses of atropine. There has been much argument as to whether or not this is due to the depression of sweating, to increased restlessness or to a direct stimulation of a heat-regulating center in the central nervous system. It has been adequately demonstrated that the hypothalamus is intimately concerned with the mechanism of heat production and heat loss, and that the control can be influenced by drugs (Masserman,⁶⁹ 1937, studying antipyretic drugs). Anterior hypothalamus lesions result in hyperthermia.

Use of methylatropine clinically in hypertrophic pyloric stenosis has produced similar results. This probably should not be considered a toxic reaction and is not considered a contraindication for either drug.

ACTION OF THE ATROPINE GROUP ON THE SYMPATHETIC SYSTEM. Bussell^{11a} (1940) reviews the rôle of atropine in relation to adrenalin and the sympathetic system. He cites the work of Meyer^{62a} (1906) who discovered that strips of ox carotid in Ringer's solution show no spontaneous rhythm, but that the addition of 6 µg. of adrenalin would cause large contractions which were in turn decreased by half if 1.5 mg. of atropine were added along with the adrenalin. Bussell was able to demonstrate that this antagonism held in perfusion of the dog's leg, the rabbit's ear, the nictitating membrane of the cat's eye, and the blood pressure of spinal cats. Atropine also caused dilatation of the spleen, of the small intestine and a fall in blood pressure in cats anesthetized with ether: all sympathetic medi-

ated actions. Hyoscine showed no similar antagonism to adrenalin. The work of Bergengren⁴ (1925) indicates that methylatropine also possesses the ability to antagonize the effect of adrenalin on blood-vessels. Atropine has been shown to cause a partial paralysis of the cervical sympathetics in the rabbit's ear perfusion experiment and of the cervical and thoracic sympathetic in studies on cats. There is no similar antagonism between atropine and posterior pituitary extract. These actions of the atropine series on the sympathetic system are not too surprising, in view of its close chemical relationship to cocaine which is a sympathetic blocking agent.

MISCELLANEOUS EFFECTS OF THE ATROPINE GROUP. These drugs are reported to have some local analgesic effects similar to those of cocaine. Edsall and Means²⁴ (1914) report that the basal metabolic rate and the respiratory quotient are not affected by these drugs. The figures of Nyman on oxygen consumption incidental to his studies on minute volume would tend to bear out this contention. Atropine as such does not affect the blood sugar level. The consensus seems to be that these drugs do not affect milk secretion but that a portion of the drug is excreted *via* the mammary gland in animals and women. It has been reported by Magaard⁶⁵ (1882) that lacrimation is decreased. Leukocytosis has been reported in children after atropine. The *voluntary* muscles of mammals are not affected in concentrations that have been tested to date.

BODILY MECHANISMS FOR HANDLING ATROPINE IN VARIOUS SPECIES. Atropine is absorbed rapidly from the gastro-intestinal tract and also disappears from the peripheral blood within a short while. Approximately one-third of the ingested dose may be recovered in the urine 14 hours afterwards. In man the balance is probably destroyed by hydrolysis to tropine and tropic acid in the liver.

Traces are detectable in other secretions including milk and sweat. These drugs readily cross the placental barrier.

Some animals possess enzymes capable of hydrolyzing atropine in the serum, brain, kidney and possibly other tissues in addition to the liver. The rabbit, an animal which is able to eat belladonna leaves without evidence of toxicity and is extremely resistant to atropine poisoning, has a high concentration of atropine esterase in its serum. Comparative studies of various tissues by Bernheim and Bernheim⁵ (1938) demonstrated atropine esterase activity in the rabbit liver and serum; guinea pig liver also hydrolyzed atropine and homatropine rapidly. The livers of the cat, rat and dog were able to hydrolyze these drugs slowly. There was no such activity in the kidney, brain or serum of the cat, rat, dog or guinea pig. Human serum was also inactive. This enzyme is not identical with choline esterase or the esterase of simple acids such as acetate. Ethylmandalate is hydrolyzed by tissues which do not hydrolyze homatropine. In all tissues tested homatropine was destroyed more rapidly than atropine. (This problem is discussed in detail by Bernheim,⁶ 1942.)

The studies of Pilcher⁷⁷ (1934) on atropine tolerance in infants and the studies of Schlossmann⁸⁰ (1937) on the relationship between age and the action of atropine do not establish this effect as directly attributable to differences in the esterases. Schlossmann comments upon the fact that infants generally show fewer central nervous system symptoms, more marked narcotic effect and unexplainable variations in resistance to these drugs. There seems to be no clinical basis for such differences. Lindberg⁶⁰ (1925) describes his experiences with the action of atropine in 100 infants. One infant was given a dose of 6 mg. without harm at the age of 8 months. There were strong vasomotor reactions in healthy infants and the production of fever even in small

doses. Definite tranquilization is produced by atropine in nervous infants.

Experimentally, rabbits of different ages were injected with atropine sulfate intraperitoneally. The LD₅₀ for rabbits under 1 month of age was 0.225 gm. per kg. body weight; that for rabbits over 1 month of age was 0.35 gm. per kg. Rabbits of different ages showed different effects from poisoning. Thus, in the 1st week of life their response to toxic doses was central nervous system paralysis. From the 2nd to 4th week in life, clonic and tonic convulsions were the prominent symptoms with poisoning. Thus, in the first week of life their response to toxic doses was central nervous system paralysis. From the second to fourth week in life, clonic and tonic convulsions were the prominent symptoms with poisoning. Older rabbits showed an increase in heart rate and respiratory rate followed by respiratory paralysis.

THE TOXICITY OF METHYLATROPINE. As might be expected, the toxic reactions to methylatropine nitrate (eumydrin, metropine) are similar in type to those of atropine from which it is derived. Reports both as to its clinical and its experimental toxicity vary. For example, it has been quoted and requoted in the literature that eumydrin is one-fiftieth as toxic as atropine (see Sollman, *Manual of Pharmacology*, 1942), apparently on the basis of Brown and Frazer's work,¹⁰ in 1869, which was on methylatropine iodide (not nitrate) and on unpublished experiments done by Paul Drucker of Rigshospitalet, Copenhagen, Denmark, in 1927. Usener³² (1926) quotes Dresser without reference as follows: Lethal dose of atropine 0.1 mg. per kg. in adults; 0.01 mg. per kg. for children; in animals (species not specified) eumydrin was lethal in doses of 0.1 gm. per kg. Kostin (also cited without reference) says that 0.15 gm. per kg. of eumydrin produced death without convulsion (differing from atropine) by paralysis (similar to curare) in rabbits.

Experiments by Graham and Lazarus³⁸ (1940) indicate, on the basis of intraperitoneal injections of white mice, that eumydrin is 3 times as toxic as atropine. The LD₅₀ of methylatropine nitrate is 0.11 gm. per kg. body weight, while the LD₅₀ of atropine is 0.32 gm. per kg. body weight. They quote Willberg's figure¹⁰² (1914) for atropine in the mouse, LD₅₀ of 0.3 to 0.4 gm. per kg. body weight, as tending to confirm their result. Fromherz³² (1937) gives the following results for atropine: lethal doses of atropine in gm. per kg. body weight for the mouse, subcutaneously 0.55 gm., intravenously 0.07 gm., orally 0.4 gm.; for the frog, subcutaneously 1.25 gm.; for the rabbit, subcutaneously 0.5 gm., intravenously 0.05; for the cat, subcutaneously 0.13 gm. He compares and comments on the variability of toxicity in various species, particularly the resistance of rodents to atropine. In man, atropine kills by its effect on the central nervous system and is 100 to 500 times as toxic as it is in rodents.

Dyson²³ (1928) argues that the effectiveness of eumydrin is due to the fact that as a dimethyl quarternary ammonium salt, it diverts the action from the rest of the nervous system to the peripheral nerve endings. This may partly explain the divergent opinion of the toxicity of this drug. Studies of Ing, Dawes and Wajada⁵⁰ (1945) on the relative potency per molecule in mydriatics showed eumydrin to be 2.22 times as active as atropine in producing mydriasis in the mouse after intraperitoneal injection, but only $\frac{1}{2}$ to 1 time as effective when applied locally to the cat's eye. This difference in mydriatic activity is of the same magnitude as the difference in toxicity of the 2 drugs for the mouse as described by Graham and Lazarus³⁸ (1940). Death from eumydrin in the Graham experiments was by general paresis and respiratory failure following an initial increase in respiratory rate. No convulsions were observed.

Ing *et al.*⁵⁰ argue that the effect of these alkaloids depends on the method of administration. They drew the conclusion that the quarternary methyl salts of the alkaloids (eumydrin) are more active than corresponding tertiary bases (atropine), but that onium salts penetrate all membranes more slowly than tertiary bases, which exist not only as salt cations but also as free base. The effect of age, the rôle of neutralizing agents in the serum, and optical isomerism (eumydrin is racemic) have not been specifically studied as they have been for atropine (Pilcher,⁷⁷ 1934; Schlossman,⁸⁰ 1937; Cushny,¹⁸ 1920; and others).

Clinically, methylatropine nitrate has been given to infants with hypertrophic pyloric stenosis over periods of weeks with only occasional tonic reactions. Lindberg's⁸⁰ (1925) studies on the elimination of atropine probably should hold fairly well for eumydrin. Most of the drug is eliminated in the urine, and the state of hydration, or rather dehydration, was a factor in practically all toxic reactions reported. 'One death with hyperpyrexia was reported by Friedlander³¹ (1934) and was attributed to idiosyncrasy. Monrad⁷¹ (1928), using a relatively large dose of 3.5 mg. per day, had 9 toxic reactions in 64 cases, consisting of nystagmus, dilated pupils, fever, flushing, restlessness, and convulsions.' Wallgren⁹⁵ (1940) described a flushing of the face as a reliable sign of early toxicity when using alcohol eumydrin applied to the tongue. Mackay⁶⁴ (1941) felt that abdominal distention was an important toxic sign and should be watched for. Fifteen of her 40 cases showed mild reactions with doses under 3 mg. per day. Reactions consisted of slight fever, rapid pulse, increased respiration rate, dryness of the mouth, bright red flush and dilated pupils. Vertue⁹⁴ (1939) reported no toxic symptoms in 21 cases, using doses of 1.25 mg. per day for 11 weeks. One of Dobbs⁷² (1939) 20 cases showed flushing when

getting 4 mg. per day. Braithwaite⁸ (1938) and Findlay³⁰ (1938) discuss 27 cases without evidence of toxicity in dosages of about 3.0 mg. per day. Svensgaard⁸⁵ (1935) reports only a few transient reactions as evidenced by clear flaming red skin and a fever of 38° while treating 61 cases with an average dose of 1.75 mg. per day of eumydrin. All reactions, except the death reported by Friedländer³¹ (1934), were transient and cleared up when drug was omitted for a short time.

RELATION OF DOSAGE TO ACTIVITY. What then are effective doses of atropine? Henderson⁴⁵ (1923) gives some pertinent information on this point. He studied the sensitivity of various nerve endings to atropine and found that the endings (response) of the bulbosacral autonomic outflow are rendered ineffective in the following order: cardiac vagus, chorda secretor, chorda vasodilators, intestinal vagus and bladder. They are depressed in the following order in a 10 kg. dog: (1) 0.1 mg. depressed the chorda secretor from 15 to 10 drops of saliva. (2) 0.2 mg. rendered the cardiac vagus less effective and 0.5 mg. eliminated vagus activity with a consequent increase in heart rate. (3) 0.1 to 0.2 mg. caused a distinct decrease in the tone of the pylorus and small intestine. (4) 0.2 mg. caused a decrease in bladder tone while 0.3 eliminated bladder tone due to vagus. (5) 0.5 mg. dilated the pupil but it was still reactive to light and convergence; maximum dilatation was secured with 0.6 mg. (6) 0.7 mg. caused a slight decrease in blood flow from the salivary gland on chorda stimulation as compared with before atropine. (7) With 30 mg., vagus stimulation produced little if any increase in the rhythmic movements of the small intestine while peristalsis was slight or absent. (8) Doses of 100 mg. caused no decrease in the isotonic or isometric contractions of the bladder on sacral stimulation.

Doses of atropine in a 65 kg. man pro-

duced the following effects: 0.2 mg. caused a decrease in nasal secretion; 0.3 mg. caused dryness of the mouth and relieved griping from constipation; the pupil was not affected. A dose of 2 mg. caused an increase in heart rate to 150 and dilatation of the pupil. Methylatropine is described as having equivalent peripheral effects or possibly stronger curare-like activity than atropine. Yet as with any drug, the effective dose is the dose necessary to produce the desired therapeutic effect. These drugs can only depress or increase the normal activities of various susceptible cells. The clinical impression of a great variability in the response that various individuals show to these drugs is amply confirmed in the wide variability found in the laboratory by the pharmacologists.

Summary. 1. The chemical structure, pharmacologic actions, toxicity and therapeutic uses of atropine, methyl atropine nitrate and related compounds are discussed.

2. The most marked difference between the 2 first-named compounds is in their effects on the central nervous system. Atropine produces marked psychic side effects even in the usual therapeutic range of dosages, whereas methyl atropine does not. Death from atropine is preceded by convulsions. Death from methyl atropine is due to paralysis and failure of respiration without convulsions.

3. The peripheral actions of the 2 compounds are apparently similar, but the

responses vary with the route of administration. Methylatropine has the weaker action in equivalent doses when applied *topically* as in ophthalmic use. Apparently, *oral* potency is approximately equal, although some investigators state that atropine is 3 or 4 times stronger. *Parenterally* methylatropine is probably somewhat stronger than atropine.

4. The essential action of both compounds is antispasmodic and they apparently prevent effector cells from reacting to acetylcholine.

5. The compounds are discussed in some detail in relation to each system of the body as follows: eye, respiratory tract, heart, salivary gland, esophagus, stomach, pylorus, small intestine, colon, smooth muscle, biliary duct tract, gall bladder, uterus, urinary bladder, sweat glands, and sympathetic nervous system.

6. The animal body probably detoxifies these compounds by hydrolysis to tropine and tropic acid. The existence of atropine esterases has been confirmed in many animal tissues. This enzyme may be unable to act on methylatropine.

7. It has long been repeated that methylatropine is only one-fiftieth as toxic as atropine. By intraperitoneal injection recent experimental evidence shows it to be 3 times as toxic for white mice as is atropine.

8. The principal clinical use to date of methylatropine has been in hypertrophic pyloric stenosis and in infantile pyloric spasms.

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BOOK REVIEWS AND NOTICES

HISTOPATHOLOGIC TECHNIC. By R. D. LILLIE, M.D., Medical Director, U. S. Public Health Service. Pp. 300. Phila.: Blakiston, 1948. Price, \$4.75.

THIS book should prove of value to all who are concerned with the preparation of tissue sections. The author admittedly does not attempt to present an encyclopedia of tissue technique, but rather is concerned with what in his opinion are the best methods for each particular purpose. The book is conveniently arranged so that stains for the various histologic structures are grouped together. In addition to the standard procedures given in most other books on the subject, there are excellent chapters on the staining of enzymes and pigments. These and many other special techniques, which are frequently neglected in laboratory manuals, are readily available in this book.

A. R.

SEXUAL BEHAVIOR IN THE HUMAN MALE. By ALFRED C. KINSEY, Prof. of Zoology, WARDELL B. POMEROY, Research Assoc., and CLYDE E. MARTIN, Research Assoc., Indiana Univ. Pp. 804. Phila.: W. B. Saunders, 1948. Price, \$6.50.

THIS book is one of the most important recent contributions to the study and understanding of the fundamental biologic problem of sex in man. Sexual histories of 5300 males have been thoroughly analyzed, and are objectively and statistically evaluated. This male group represents a very adequate cross-section of our male population, as it includes large numbers from nearly all educational and social levels. The text includes brief reviews of results of other workers in this field, a study of the statistical methods used, and techniques involved in obtaining an adequate sexual history. Variations in sexual activity with social and educational classes, age and religious background are correlated and explained. Practically all possible sources of sexual outlet are considered with respect to incidence in various groups, techniques and social implications.

The problem of male sexual behavior has

been soundly and keenly attacked from all angles; the results obtained—unbiased and objective statistics—are very instructive and occasionally revelational. I. Z.

THE PATHOLOGY OF TRAUMATIC INJURY. A GENERAL REVIEW. By JAMES V. WILSON, M.D., M.R.C.P. (Lond.), Pathologist to Harrogate and District General and Royal Bath Hosps., D.A.D.P., Malta Command, 1940-1943. Pp. 192; 61 ills. Balt. and London: Williams & Wilkins, 1946. Price, \$6.00.

THIS small volume is based on the author's experience with the Royal Army Medical Corps in the Second World War. Intended as a general review, it aims to "mention progress and at the same time outline difficulties and problems awaiting urgent solution, to deal with essentials rather than give a mass of irrelevant facts."

Though written abroad, under difficulties, and drawing its material chiefly from the traumata incident to modern war, the book for the most part achieves its goals. Best covered are the effects of blast, the rediscovered "crush syndrome" and the increasingly recognized embolism of fat. There is a chapter on burns, but effects of war gases and atomic weapons are not considered. A modest number of references up to 1946 serve as a basis for modern ideas.

The predominantly surgical viewpoint, with many pages of advice on diagnosis and treatment, is distracting in a book with this title. The surgeon's inferences on therapy may be quite different from those of the pathologist, who is not responsible for the care of injured patients. It is hoped this point will be given consideration in a later edition. C. B.

NUCLEIC ACID. SYMPOSIA OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY. No. I. Edited by J. F. DANIELI and R. BROWN. Pp. 290; 18 ills. Cambridge, at the University Press; New York: Macmillan, 1947. Price, \$8.50.

THIS book is a collection of papers read at a symposium in July, 1946. The various experimental approaches to the study of nucleic acids are considered and evaluated by such eminent workers as Danielli, Caspersson, Brachet, Darlington, Gulland, and many others. The biochemical structure and methods of synthesis of nucleic acids and their purine derivatives are thoroughly reviewed. The various histochemical techniques used for the identification of nucleic acids are described and criticized in detail. Among other studies of nucleoproteins are included histochemical observations on tumor tissue, the relationship of nucleoprotein metabolism to nerve function, x-ray studies and effects, and the function of nucleoprotein in the cell nucleus. Most of the papers treat comprehensively one or several aspects of nucleoprotein study and the results achieved. Knowledge of nucleoproteins is thus effectively concentrated in this excellent text.

I. Z.

DISEASE OF THE NOSE, THROAT AND EAR. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., Late Prof., Univ. of Illinois School of Medicine, and HOWARD CHARLES BALLENGER, B.S., M.D., F.A.C.S., Assoc. Prof. of Otolaryngology, Northwestern Univ. School of Medicine. Assisted by JOHN JACOB BALLENGER, B.S., M.D. 9th ed. Pp. 993; 597 ills.; 16 plates. Phila.: Lee & Febiger, 1947. Price, \$12.50.

The latest revision of this standard work brings the text and illustrations up to date. New chapters dealing with headache, neuralgias of the face and head, and rhinoplastic surgery have been added. Authoritative revisions of the section on bronchoscopy, laryngoscopy, esophagoscopy and gastroscopy have been carried out by Gabriel Tucker and C. L. Jackson, while those on the physiology and functional tests of the labyrinth and inflammatory diseases of the labyrinth were contributed by Alfred Lewy.

Embracing the entire field of otolaryngology, the book employs the orthodox method of approaching each disease by first presenting the fundamental anatomical, physiological and pathological considerations, and then discussing etiology, symptoms, diagnosis and treatment. The therapeutic suggestions are those which meet the acid tests of time and practice. The authors have appreciated the

instruction value of illustrating the instrumentarium for various surgical procedures.

Controversial subjects have been avoided. A frank discussion of a few of these, such as the present role of vitamin therapy in otolaryngology, might have been profitably introduced as a guide to students and general practitioners. Most of the bibliographical references are arranged at the foot of the page so as to be readily accessible. The value of a reference volume of this scope and magnitude, however, would be enhanced by a more complete bibliography.

This work, both comprehensive and condensed, continues to be a leader in its field and invaluable to the medical student, the general practitioner and the otolaryngologist.

H. S.

UNIPOLAR LEAD ELECTROCARDIOGRAPHY. By EMANUEL GOLDBERGER, B.S., M.D., Clinical Lecturer in Medicine, Columbia University, Faculty of Medicine. Pp. 182; 88 ills. Phila.: Lea & Febiger, 1947. Price, \$4.00.

This monograph is the result of several years' study to determine the practicability of routine clinical use of unipolar leads and the correlation of unipolar extremity leads, precordial leads and the standard leads. The author is well qualified by training and experience to present this subject. The approach to the interpretation of the electrocardiogram is made in terms of basic unipolar lead patterns, rather than standard limb lead patterns, as is the rule in most texts.

The theoretical considerations of the clinical use of unipolar leads are based largely on the Einthoven triangle theory. The author advocates the routine use of 6 unipolar precordial leads, 3 unipolar extremity leads (or "augmented" unipolar extremity leads), and the usual limb leads. Special emphasis is placed on the variations in the unipolar extremity leads and standard limb leads which occur with changes in position of the heart. The author believes that the use of unipolar leads is of particular advantage in the following conditions: The interpretation of axis deviation; the diagnosis of Q wave abnormalities, especially Q3 waves; the differentiation of pulmonary embolism and posterior infarction; the diagnosis of small or multiple infarcts; the differentiation of bundle branch block; the diagnosis of right ventricle hypertrophy, and the interpretation of abnormalities of the RS-T segments and T waves.

Evidence is offered in support of the au-

thor's theses, and the illustrations are adequate and clear. (Incidentally, an error was noted in the correlation of the text with Figure 41B.) The theoretical aspects of the subject are presented in a manner that can be grasped by the average physician. Some of the interpretations of patterns obtained from ventricular hypertrophy with variations in the position (and rotation) of the heart may be questioned by other authorities. The last word has not been spoken on many phases of the subject, and one must agree with the author when he says "the significance of many electrocardiographic changes is still obscure, even in the unipolar leads." The monograph is a distinct contribution to the field of electrocardiography and should be read with interest and profit by all cardiologists and internists. J. V.

OFFICE TREATMENT OF THE EYE. By ELIAS SELINGER, M.D., Attending Ophthalmologist, Mount Sinai, Cook County and Michael Reese Hosps. Pp. 542; 67 ills. Chicago: Year Book Publishers, 1947. Price, \$7.75.

This book is a very practical handbook of treatment intended for practicing ophthalmologists. There are excellent sections on the general aspects of chemotherapy, errors of refraction and the usual diseases of the eye and its adnexa. It is pleasing to see that where modern treatment has effectively replaced older procedures, this book recognizes the fact by omitting them. The illustrations are excellent. F. A.

400 YEARS OF A DOCTOR'S LIFE. Collected and Arranged by GEORGE ROSEN, M.D., and BEATE CASPARI-ROSEN, M.D. Pp. 429. New York: Henry Schuman, 1947. Price, \$5.00.

The authors have achieved an interesting experiment in biographical montage. For this anthology of the arc and the stations of the physician's existence, they drew on "more than eighty personalities (four of them women) who have made significant contributions to the literature of medical autobiography."

The organization of the text is unique. Under a dozen such headings as Early Years; Scientist; Scholar; Teacher; The Doctor as Patient; The Doctor Goes to War; Writing and Politics, the authors collate from several different sources what each of the personalities had written on the particular score. This arrangement affords us the memories of their

early years, as reported by such divergent authors as Daniel Drake, Havelock Ellis and Santiago Ramon y Cajal, and the reflections on life and death of the 21 year old Virehow, the despairing Horace Wells, the life-wise Walter Cannon, and the stoical Hans Zinsler.

The effect of such collations is at times puzzling and provocative, but always interesting. The one conviction that emerges is that there is no medical prototype, no "homo medicus." Physicians differ in origins, in constitutional and personality types, in experiences, and in all else, as widely and as ardently as do all men in all things. Save perhaps for their devotion to their profession, there is no distinguishing common denominator among doctors. The sum of the personal experiences of the "eighty personalities" abstracted in the Rosen anthology does not, to this reviewer's mind, yield a "composite autobiography of The Doctor".

But the Rosen anthology yields more real and more valuable assets. It provides good reading, both in the biographical notes which precede each citation, and in the citations selected. It provides good sampling, to inform and to sharpen one's interest in distinguished men and women who have served in the most humane and compassionate of professions. It is a fine volume for random reading, and a fine guide to the best in medical autobiography. I. G.

BLOOD DERIVATIVES AND SUBSTITUTES. By CHARLES STANLEY WHITE, M.D., Sc.D., Former Prof. of Surgery, George Washington Univ. School of Medicine, and JACOB JOSEPH WEINSTEIN, B.S., M.D., Assoc. in Surgery. Pp. 484; 190 ills. Balt.: Williams & Wilkins, 1947. Price, \$7.50.

The title of this book of 15 chapters amply summarizes the scope of the contents. Following an introductory historical chapter, some aspects of the chemistry and physiology of plasma are presented, with much of the space given to commonly employed laboratory methods. Chapters dealing with preparation, storage and administration of plasma, plasma fractions and by-products, whole blood and substitutes, are complete in details and generously illustrated. The last third of the book deals with the etiology and treatment of shock, and the results of plasma therapy. Throughout the book points of clinical interest are usually illustrated with case reports.

Most of the facts required for operating a

blood and plasma bank and the principles necessary for their intelligent use are to be found. One question, however, the need for including laboratory procedures which may be found in any book of laboratory technique. A serious deficiency is the absence of an adequate treatment of blood groups and the Rh factor. Under the heading of "Infectious Jaundice" reports on the apparent transmission of jaundice by blood or plasma are cited (p. 463), but the importance of homologous serum jaundice has apparently escaped the authors since they do not discuss the desirability of using unpooled plasma. R. N.

INFANT NUTRITION. By P. C. JEANS, A.B., M.D., Prof. of Pediatrics, College of Medicine, State Univ. of Iowa, and WILLIAMS MCKIM, MARRIOTT, B.S., M.D., Late Prof. of Pediatrics, Washington Univ. School of Medicine. 4th ed. Pp. 495; 36 ills. St. Louis: C. M. Mosby, 1947. Price, \$6.50.

This text contains in very readable form a good combination of fundamental nutritional information together with many practical points for the application of such information. The facts have been brought up to date and are presented in a thoroughly sound and effective way. K. E.

INTERNAL MEDICINE IN GENERAL PRACTICE. By ROBERT PRATT MCOMBS, B.S., M.D., F.A.C.P., Asst. Prof. of Medicine, Tufts College Medical School, etc. 2nd ed. Pp. 741; 122 ills. Phila., and London: W. B. Saunders, 1947. Price, \$8.00.

The author has attempted to present a short, practical book on internal medicine for the general practitioner, stressing particularly methods of diagnosis. This edition contains much useful information in the form of tables of differential diagnosis and indications for and techniques of important diagnostic aids. It is up to date and embodies a thorough and thoughtful approach to the problems of internal medicine. Many practical hints are scattered throughout. The arrangement of the material is good and the amount of space allotted to the various diseases corresponds more nearly to their incidence in practice than in the usual text book of medicine.

Turning to shortcomings, in a few instances, such as the use of digitalis in congestive heart failure, the methods of administration of a drug are not specific enough. In some diseases,

such as ulcerative colitis and glomerulonephritis, not enough information as to the clinical course is given to permit intelligent management.

In general, however, this revised book should prove a useful addition to the library of the practitioner of general medicine for whom it was intended. It also has much to recommend it as a book for the fourth year medical student or intern. A. R.

HANDBOOK OF PSYCHIATRY. By WILLIAM OVERHOLSER, M.D., Prof. of Psychiatry, George Washington Univ., and WINFRED V. RICHMOND, M.D., Late Chief, Department of Psychology, St. Elizabeth's Hosp. Pp. 252. Phila.: J. B. Lippincott, 1947. Price, \$4.00.

PSYCHOLOGY and psychiatry are interwoven in this book in a refreshing and sincere manner. The authors have put the various types of human behavior and motive into terms comprehensible by the average college student, meanwhile accomplishing a hitherto unattempted correlation of the several "schools of thought" of psychiatry with psychology, general medicine, and allied sciences.

The chief source of clinical material was St. Elizabeth's Hospital, which has actively treated patients from all of the United States and its possessions. This wealth of clinical material comes into the text in the form of abstracts of case histories, skillfully prepared and selected.

While the book as a whole is outstanding, the chapters dealing with the modern mental hospital, mental aberrations of war, forensic psychiatry, child psychiatry and "psychiatry and the layman" are especially recommended. The fourth chapter, dealing with mental deficiency, despite confusing use of terminology, is unparalleled in similar texts.

The authors acknowledge that crusading laymen, following the example of Dorothea Lynch Dix, to whom this book is dedicated, were largely responsible for and should be credited with much of the early advances in the field of psychiatry. They hope that "in the campaign for the development of better human beings, for raising the level of our human resources" psychiatrists may depend upon the backing of a body of informed public opinion, without which psychiatrists would be "as helpless as a general without an army."

There is an excellent bibliography.

E. B.

NEW BOOKS

The Sulfonamides and Allied Compounds. By ELMORE H. NORTHEY, Ph.D., American Chemical Monograph Series. Pp. 660. New York: Reinhold, 1948. Price, \$12.50.

Occupational Medicine and Industrial Hygiene. By RUTHERFORD T. JOHNSTONE, M.D., Consultant in Industrial Health, Lecturer, Univ. of California. Pp. 604; 117 ills., 7 in color. St. Louis: C. V. Mosby, 1948. Price, \$10.00.

Tuberculosis. By FRANCIS MARION POTTENGER, M.D., F.A.C.P., Emeritus Prof. of Medicine, Univ. of Southern California. Pp. 598; 105 ills. St. Louis: C. V. Mosby, 1948. Price, \$12.00.

Brief Psychotherapy. By BERTRAND S. FROHMAN, M.D., with the collaboration of EVELYN P. FROHMAN. Foreword by WALTER C. ALVAREZ, M.D. Pp. 265. Phila.: Lea & Febiger, 1948. Price, \$4.00.

Proteins and Amino Acids in Nutrition. Edited by MELVILLE SAHYUN, M.A., Ph.D. Pp. 566. New York: Reinhold, 1948. Price, \$7.50.

The Rh Factor in the Clinic and the Laboratory. Edited by JOSEPH M. HILL, M.D. and WILLIAM DAMESHEK, M.D., Special, Issue No. 2 of Blood, *The Journal of Hematology*. Pp. 192. New York: Grune & Stratton, 1948. Price, \$4.25.

Deep Analysis. By CHARLES BERG, M.D. (LOND.), D.P.M., Fellow of the British Psychological Association. Pp. 254. New York: W. W. Norton, 1947. Price, \$3.50.

Atlas of Bacteriology. By R. CRANSTON LOW, M.D., F.R.C.P.E., F.R.S.E. (EDIN.), and T. C. DODDS, F. I. M. L. T. 168 ills., 167 in color. Balt.: Williams & Wilkins, 1947. Price, \$8.50.

Cardiopatías Congénitas de la Infancia. By DR. AGUSTIN CASTELLANOS Y GONZALEZ. Pp. 406; 20 ills. Havana, Cuba: M. V. Fresneda, 1948. Price, \$9.00.

Diabetes Mellitus in General Practice. By ARTHUR R. COLWELL, M.D., Assoc. Prof. of Medicine, Northwestern Univ. Pp. 350. Chicago: The Year Book Publishers, 1947. Price, \$5.25.

Diseases of the Joints and Rheumatism. By KENNETH STONE, D.M. (OXON.), M.R.C.P. Pp. 362; 58 ills. New York: Grune & Stratton, 1947. Price, \$6.50.

Experimental Air-borne Infection. By THEODOR ROSEBURY, with the co-authorship of the Staff of the Laboratories of Camp Detrick, Md. Pp. 222; 40 figs. Balt.: Williams & Wilkins, 1947. Price, \$4.00.

Applied Medical Bacteriology. By MAX S. MARSHALL, Ph.D., with the collaboration of JANET B. GUNNISON, M.A., ALFRED S. LAZARUS, Ph.D., ELIZABETH L. MORRISON, M.A., and MARIAN C. SHEVKY, A.B., Medical Center of the Univ. of California. Pp. 340; 8 ills. Phila.: Lea & Febiger, 1947. Price, \$4.50.

The Pathology of Nutritional Disease. By RICHARD H. FOLLIS, JR., M.D., Assoc. Prof. of Pathology, Duke Univ. School of Medicine. Pp. 291; 71 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

Advances in Military Medicine. Science in World War II. Edited by E. C. ANDRUS, D. W. BRONK, G. A. CARDEN, JR., C. S. KEEFER, J. S. LOCKWOOD, J. T. WEARN, W. C. WINTERNITZ, and TUCKERMAN DAY. Foreword by ALFRED N. RICHARDS. In 2 vols. Pp. 900; 94 figs. Boston: Little, Brown, 1948. Price, \$12.50.

The Biology of Melanomas. Edited by ROY WALDO MINER, MYRON GORDON, and LOTHAR SALIN. Vol. IV. Pp. 478; 107 plates. New York: The New York Academy of Sciences, 1948. Price, \$5.00. To members, \$4.00.

Blue Cross and Medical Service Plans. By LOUIS S. REED. Pp. 323. Washington, D. C.: U. S. Public Health Service, 1947.

Telepathy and Medical Psychology. By JAN EHRENWALD, M.D. Pp. 212. New York: W. W. Norton, 1948. Price, \$3.00.

Case Histories in Clinical and Abnormal Psychology. Edited by ARTHUR BURTON, Assoc. Prof. of Psychology, Willamette Univ., and ROBERT E. HARRIS, Assoc. Prof. of Medical Psychology, Univ. of California. Pp. 680. New York: Harper & Brothers, 1948. Price, \$4.00.

NEW EDITIONS

Disability Evaluation. By EARL D. McBRIDE, M.D., F.A.C.P., Diplomate, American Board of Orthopedic Surgery. 4th ed. Pp. 667; 400 ills. Phila.: J. B. Lippincott, 1948. Price, \$12.00.

The Treatment of Rheumatism in General Practice. By W. S. C. COPEMAN, O.B.E., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.). 4th ed. Pp. 258. Balt.: Williams & Wilkins, 1946. Price, \$4.00.

Communicable Disease Control. By GAYLORD W. ANDERSON, M.D., DR.P.H., Mayo Prof. and Director, School of Public Health, Univ. of Minnesota, and MAR-

GARET G. ARNSTEIN, R.N., M.A., M.P.H. 2nd ed. Pp. 450. New York: The Macmillan Company, 1948. Price, \$5.00.

Endotracheal Anæsthesia. By NOEL A. GILLESPIE, M.A. (OXON.), M.D. (WIS.), Assoc. Prof. of Anæsthesia, Univ. of Wisconsin. 2nd ed. Pp. 237; 56 figs; 1 color plate. Madison: University of Wisconsin Press, 1948. Price, \$4.00.

Treatment by Diet. By CLIFFORD J. BARBORKA, M.D., D.Sc., F.A.C.P., Asst. Prof. of Medicine, Northwestern Univ. Medical School. 5th ed. Pp. 784; 14 ills., 13 in color. Phila.: J. B. Lippincott, 1948. Price, \$10.00.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ORIGINAL ARTICLES

AMINO-ACIDURIA IN HEPATO-LENTICULAR DEGENERATION (WILSON'S DISEASE)

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(From the Neurological Unit, Boston City Hospital and the Department of Neurology, Harvard Medical School)

THE close but undefined association between cirrhosis of the liver and a specific cerebral degeneration in the disease hepato-lenticular degeneration has excited continued interest since attention was first drawn to it by Kinnier Wilson³⁸ in 1912. The hepatic cirrhosis of this disease indicates the possible presence of a metabolic fault, elucidation of which would undoubtedly lead the way to a better understanding of more than one type of chronic degeneration of the brain. Despite many investigations, the nature of the *noxa* in Wilson's disease has remained unknown. It is not even determined whether the brain is damaged by some substance produced by the damaged liver, or if both brain and liver suffer from the same agent.

The present report offers evidence derived from a type of case which appears crucial to the point of issue, namely a well defined but mild example of the disease without obvious liver damage. Since this mild chronic "pseudosclerotic" type of the disease is not generally recognized and

since investigators of hepatic disorder may also wish to take advantage of its characteristics, it is necessary first to describe in some detail its place in the whole group of disorders that comprise hepato-lenticular degeneration. For more detailed discussion of the other aspects of the disease the reader is referred to a recent review by one of us.⁸

Hepato-lenticular degeneration is a familial disease, affecting nearly all the siblings in one generation, and doubtfully if ever giving evidence of either cerebral or hepatic disorder in the preceding generation. It usually develops in adolescence, and the earliest reported case began at the age of 4 years. It is thus clearly demarcated from erythroblastosis fetalis and kernicterus. Recent studies on some of our cases failed to show any clear relationship to Rh incompatibility. It is a progressive disease, but often intermittently so. The hepatic cirrhosis may be frank and persist long before nervous symptoms arise. Indeed some succumb to the cir-

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rhosis without ever developing the neurological disorder, and in such cases the disease has been identified only by its complete development in siblings. In most patients with the fully developed disease the cirrhosis has not given rise to other than doubtful digestive symptoms. In the analysis of the literature by André,¹ of 145 cases verified by the presence of Kayser-Fleischer ring or by proven family history, 110 fell into this group of "latent" cirrhosis. In 27 cases in this series (18.5%) the hepatic symptomatology had been intensely manifested, and in 7 cases (5%) the hepatic illness had occurred without neurological disorder. Only the case of Wimmer³⁹ presented neurological symptoms without either macroscopic or microscopic evidence of cirrhosis at autopsy. André¹ further accepts the cases of Eicke¹⁰ and of Froelich and Harbitz,¹² however, as instances of absence of cirrhosis in the presence of cerebral lesions, though the diagnostic criteria had excluded them from the larger group analyzed above. Thus the association of hepatic cirrhosis and cerebral lesions, though close and numerically frequent, is not absolute.

Attempts to demonstrate histological changes in the brain in association with more common types of cirrhosis have been unsuccessful in the experience of the Hursts¹⁹ and others. Only Schaltenbrand²⁹ and Scherer³⁰ found glial cells resembling those of hepato-lenticular degeneration. Damage to the liver, experimentally produced, was found to be associated with lesions of the central nervous system by some investigators^{20,23} but the type of damage was unspecific. In its mildest form the change in the central nervous system in established hepato-lenticular degeneration is also unfortunately non-specific, for the distinctive giant glial cells of Alzheimer are then not present. The changes found in the liver in Wilson's disease have been greatly varied, as has been the associated hepatic history. A mild chronic lobular cirrhosis of Laennec type (classified as subacute yellow atrophy by some) is commonly found, and only a

minority present early and severe evidence of portal obstruction. There is great variation in the size of regenerated nodules. Four cases are reported in whom the spleen had been removed under the impression that the condition was Banti's disease and another such case has recently been seen by us. Recurrent episodes of digestive disorder may long precede the onset of nervous symptoms, and in some such episodes mild jaundice occurs. Lüthy²⁴ has commented that such clinical evidence of hepatic disorder in the "hepatic stage" frequently lessens or disappears with the onset of neurological symptoms. We have not found this in cases personally observed.

The nervous symptoms also present great variation from family to family. The development of severe immobilization and disability owing to extrapyramidal rigidity, and distortion of posture, with or without tremor, appearing in adolescence is relatively well-known following the excellent description by Wilson.³⁸ Such extreme disability, with the peculiar "fatuous smile," can scarcely be mistaken for any of the more common nervous diseases. There have been very few reports in English of another variety with remarkably different clinical aspect, namely "pseudosclerosis," which is commonly mistaken for multiple sclerosis or post-encephalitic Parkinsonism. This variety has been frequently reported in the German literature, reviewed by Hall¹⁴ and Lüthy.²⁴ An unusual type of tremor may be its sole neurologic sign. Whereas "progressive lenticular degeneration" as described by Wilson³⁸ appears in adolescence and progresses to a fatal termination in a period of months or perhaps 1 or 2 years, the "pseudosclerosis" of Westphal,²⁵ Strümpell,²³ and Fleischer¹¹ appears at any time from the second to the fourth decade and commonly runs a chronic course of many years in duration. In distinction from the gross cavitation in the brain of Wilson's cases, "pseudosclerosis" is often associated with no change visible to the naked eye, and only a peculiar disorder of

the glia has been regularly demonstrated microscopically. The identity of the two syndromes was, however, firmly established by Hall¹⁴ who first proposed the name "hepato-lenticular degeneration" to cover both varieties. The very characteristic pigmentation of the cornea ("Kayser-Fleischer Ring") has been present in all cases of the pseudosclerotic variety, but in only about 60% of "progressive lenticular degeneration." It has not been found in any other condition. Its absence in any given case may, therefore, be related to brevity of the total duration of the illness. Strict scrutiny of the neurologic and pathologic data and family history is then necessary to establish the disease.

The differences between the different types of the disease have a fairly close but not absolute relationship to its rate of evolution. Thus fulminant examples reaching extreme degrees of hepatic and nervous disintegration in the course of one¹⁸ to several months have been recorded in young children, whereas Lüthy's²⁴ Case 2 of pseudosclerosis had the tremor for 43 years. As in many other familial diseases, the type and course of the disease remains relatively constant within any particular family.

The tremor, which may be the only neurologic symptom of the pseudosclerotic variety of the disease, presents a very characteristic flapping movement of the outstretched hands, which are alternately flexed and extended at the wrists ("wing-flapping") of 3 to 5 beats a second. At times the whole arm beats up and down from the shoulder (the "swimming" movement of Strümpell). Some patients have none of the shoulder movement, some more. The tremor seldom involves the elbow joint, and only at times or in a late stage do the fingers beat. Individual digits then may beat separately. At first, and in some for the whole course of the disease, the upper limbs are alone affected by the tremor. From the beginning the tremor is increased by voluntary movement, as is that of cerebellar incoördination, and the patient complains primarily

of difficulty in bringing a fork or glass of water to the mouth. When there is emotional stress the upper limbs show a rhythmical tremor at rest, but the tremor is more easily abolished by complete relaxation than is that of Parkinsonism. The tremor has the same characteristics in both types of the disease, but in the progressive lenticular type a resting tremor of Parkinsonian type is added in later stages. The occurrence alone of action tremor, beginning in the 3rd or 4th decade of life, is the characteristic feature of the chronic form of pseudosclerosis. We have discussed the pathogenesis of the tremor elsewhere,⁸ pointing out that its cerebellar character indicates that it more probably results from the degenerative changes in the dentate and red nuclei almost constantly present, rather than from the lesion of the basal ganglia. Dysarthria is also commonly reported.

We have described these peculiarities of the disease at some length, because the family reported here is one of 2 brothers who show the late and milder pseudosclerotic form of the disease. The action tremor of the arms, the titubation of the head and trunk, and the ataxic gait would pass for a condition of cerebellar atrophy, of late familial type, were it not that the tremor is predominantly in the hands. Both brothers present an unusually well developed orange-green Kayser-Fleischer ring.

Laboratory tests designed to demonstrate the presence of the liver disorder in hepato-lenticular degeneration have given equivocal results. André¹ has made a detailed analysis of the findings in 147 reported cases. The older laboratory tests for hepatic function such as levulose tolerance, galatose tolerance, tests for bile salts and for bilirubinemia have been frequently reported negative in cases of hepato-lenticular degeneration. Urobilin and urobilinogen has often been found in the urine but not in at least 7 authentic cases. As might be suspected from the usual intermittent course of the disease the results of tests have fluctuated and have

given unequivocal evidence only when severe hepatic dysfunction has been obvious from clinical data. Sweet, Gray, and Allen³⁴ found that the serum colloidal gold reaction of Allen¹³ was sensitive enough to give a positive reaction on the absence of hepatic symptoms. In this clinic Homburger and Kozol¹⁷ recently reported comparative tests by newer techniques on 2 families under our observation. The cephalin-flocculation test of Hanger¹⁵ gave the most constantly positive results, but considerable fluctuation was present, even in a patient with a chronic pseudosclerotic form of the disease beginning at the age of 30 years. That the presence of severe liver damage in any form could be associated with a positive result renders such tests non-specific.

In recent years it has been established that disequilibrium in amino-acid metabolism, particularly a deficiency of cystein, or lack of balance of choline may lead to a fine lobular cirrhosis in animals. It is therefore of interest to inquire into the relationship of amino-acid metabolism to the cirrhosis of Wilson's disease. Unfortunately severe hepatic damage of any kind also disturbs amino-acid metabolism, so that, in order to determine whether any disorder that is found is primary or secondary, it would be necessary to establish the presence of disorder before the hepatic disease commenced. This could be done in a younger member of a known family, and liability of the patient established by follow-up. A more rapid method is to test a patient suffering from a very chronic form of the disease with minimal liver disorder. The patient described below appears to fulfill these latter requirements satisfactorily.

Case Report. J. G., a 34 year old married Italian former truck-driver was admitted to the Neurological Service of the Boston City Hospital on March 4, 1947, with the chief complaints of shaking of extremities and trunk, and difficulties of speech of 3½ years' duration. The disease had begun insidiously at a time when the patient was about 29 years old, first manifesting itself as a tremor

of his out-stretched arms, disappearing during rest and accentuated by any purposeful movement. The tremor gradually worsened until, about 2 years ago, it began to interfere with his work, so that he had to give up driving trucks. At about this time a tremor of the head and unsteadiness of the trunk also made their appearance. One year prior to admission, speech became noticeably altered. A gross tremor of the shoulders gradually developed so that 4 months before admission shaving and feeding himself had become quite impossible. In spite of the marked disability in the upper extremities he had found no difficulty in walking, while a slight tremor of the legs only became evident when the patient tried to step onto a chair. There had never been any headaches, vertigo, nausea, vomiting or localized weakness.

The patient had developed a cataract in the left eye during adolescence dating from some unremembered and doubtful injury in early childhood. This had eventually progressed to complete amaurosis in the left eye. His general health had been very good. The patient had always had a hearty appetite, had never suffered from any form of indigestion, nor had he ever been jaundiced. Melena and bloody stools were denied. There was a very moderate intake of Italian red wine, and the dietary history was essentially negative.

Family History. Inquiries regarding the family history disclosed that the patient's brother, 37 years old at present, had been suffering for the past 10 years from an identical tremor. This fact was fully confirmed on examining the patient's brother, who showed the same coarse, flapping tremor of the arms accentuated by movement, tremor of the head and trunk, the slurred-scanning speech and the classical Kayser-Fleischer rings of pigment in the outer part of the cornea of both eyes. He had also developed mild mental deterioration and was having frequent tonic generalized seizures.

The grandparents of the two brothers had died in Italy and information concerning them was not available. Their mother had died in her early thirties in Italy in 1918 of "Spanish Influenza." The patient's father, aged 68, was alive and quite healthy. The family consisted of 5 siblings 1 of whom had died in infancy, presumably of pneumonia. Of these siblings still living, the eldest had

demonstrated signs of a neurologic disease at the age of 27, as mentioned previously. He is unmarried. Two, both females, aged 31 and about 35 years were healthy, had married, and possessed healthy children. The 5th is our patient who developed symptoms at the age of 30 years. The patient's father had remarried and had 2 healthy offspring, aged 26 and 27 respectively, from this second marriage. The patient himself had 3 healthy children, 2 sons and 1 daughter. The youngest of these, however, was jaundiced at birth due to Rh incompatibility.

and in reflected light there was a slight greenish tinge. The Kayser-Fleischer rings were even more fully developed in the brother, and were in him remarkable, for the presence of a slight arcus senilis revealed clearly that the Kayser-Fleischer ring was much more deeply situated (Fig. 1). It is well known from histologic studies that the ring is in fact in Descemet's membrane lining the inner aspect of the cornea. In this patient also there was a zone of dark brown pigmentation just over 1 mm. broad on the sclerotic, surrounding the limbus (Fig. 1). This is



FIG. 1.—Photograph of the eye of the elder brother of the patient to show the Kayser-Fleischer ring of pigmentation which appears here as a broad zone of diffuse haze around the outer cornea, obscuring the iris. There is also a zone of brown pigmentation on the conjunctiva just bordering the corneo-scleral junction. The patient himself had a similar corneal ring but it was not so well developed, and was more difficult to photograph.

Physical Examination. The general physical examination of the patient disclosed a well-nourished, well-developed male in no acute discomfort. The pulse rate was 76, respirations 18 per minute, temperature 98.6° F., with a blood pressure of 138/92/mm. The left eye showed an opacity of the lens dating from an injury in childhood, pallor of the optic nerve and almost complete amaurosis on that side. The cornea in both eyes showed a zone, about 3 mm. wide, of brown pigmentation in the periphery. The ring of pigmentation was complete and was most dense near the limbus and faded into a smoky haze towards the center of the cornea. In transmitted light its color was dark brown,

extremely unusual. The complexion was dark and sallow but there was no other unusual pigmentation in either brother. The cardiovascular system was negative. The liver of our patient was just palpable at the costal margin and presented a hard, smooth, non-tender edge. The spleen was not enlarged. No evidence of collateral venous circulation was found on the abdomen. There were no spider angiomas. No hemorrhoids were detected, and there was no ascites or edema. Jaundice was not present.

Neurologic Examination. The right pupil reacted normally to light and on accommodation. The left eye showed an am-

blyopic exophoria, and the left pupil reacted very sluggishly only on illuminating the iris from the periphery. There was no nystagmus. There was no tremor of the palate or tongue, but speech was slightly slurred and scanning in character. Otherwise the cranial nerves were negative. The motor power was intact throughout. There was a

hands which flapped in coarse alternating flexion-extension at the wrists (Fig. 2). The tremor would fluctuate in amplitude sometimes appearing in one or the other hand, sometimes both. The more intense the tremor the more the two hands tended to beat in time, but often they alternated in similar rhythm of about three beats a second.

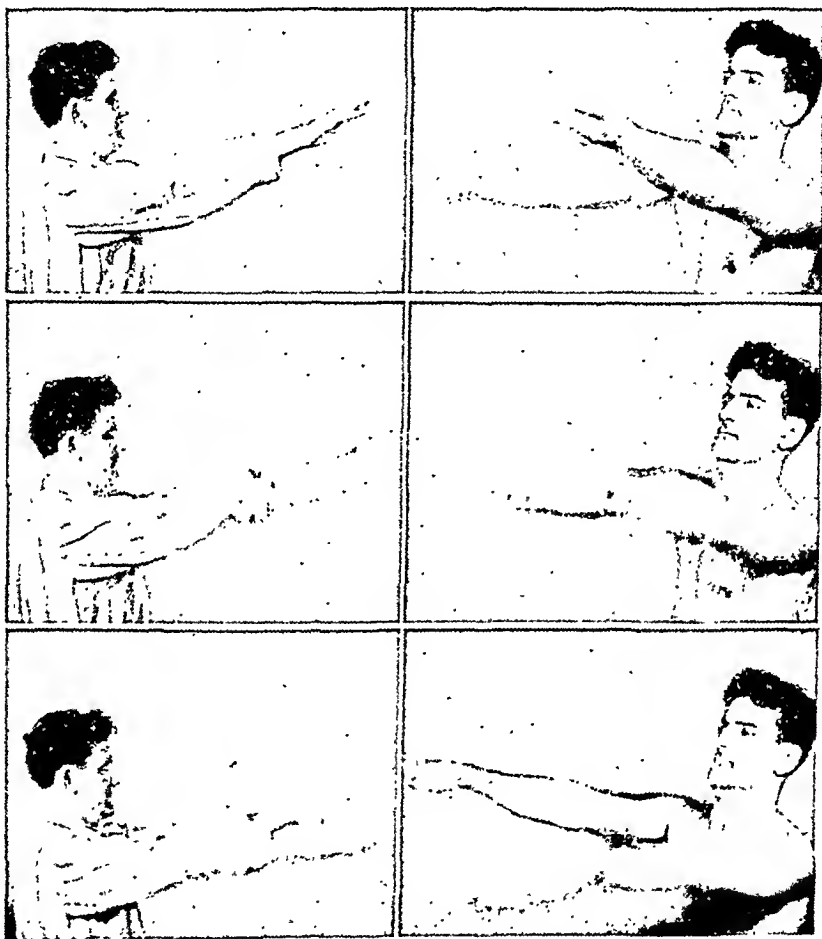


FIG. 2.

FIG. 3.

FIGS. 2 and 3.—Photographs of the patient to show the flapping tremor of the hands (Fig. 2) and of the shoulders (Fig. 3). From a cinematograph film with intervals of $\frac{1}{15}$ second between each of the series.

coarse rhythmic tremor of the head in both the antero-posterior and lateral planes, which was transmitted to the upper part of the trunk when unsupported, and which disappeared at rest.

When the patient lay with all parts of the body supported there was no tremor in any part. If the arms were outstretched, a rhythmical coarse tremor would begin in the

With any sustained or extra effort one or both arms would oscillate up and down at the shoulder (Fig. 3) in the same rhythm. With this the head would often begin to titubate more violently, so that with any severe exertion or emotional upset the whole upper part of the body would undergo violent oscillation. Electromyographic studies revealed that there was no muscular activity at rest,

and that whatever muscular group in the upper limbs was activated the discharge of action currents soon broke into rhythmical bursts. The rhythm was more fully and more rapidly developed in the deltoids and forearm muscles but was also shown in biceps and triceps. Antagonists did not enter contraction except in synergic activity and their rhythm then alternated with that of the opposing muscle.

The tremor became more severe in the course of any movement. The finger-to-nose test was usually terminated by the patient slapping his face. Alternating movements were very poorly performed. The trunk manifested slight titubation. The legs showed very slight action tremor on performing the heel-to-shin and toe-to-object tests. The gait was normal except for slight titubation and a slight hesitation in turning. The biceps, triceps and radial reflexes were present and equal, as were the abdominal and cremasteric reflexes. The knee and ankle jerks were also normal. The plantar responses were both flexor. No sensory loss of any kind could be demonstrated. Vibration and position sense were unimpaired.

Laboratory Studies. Examination of the blood showed a red-cell count of 4.97 million, hemoglobin of 100%, white-cell count of 7500 with a normal differential count. The urinalysis showed no sugar, acetone or albumen, and the sediment was negative. A marked amino-aciduria was, however, noted and this will be discussed in detail later.

The blood N.P.N. was found to be 36 mg. per 100 cc., and the fasting blood sugar was estimated as 110 mg. per 100 cc. The blood Hinton was reported as negative. Roentgen ray examination of the skull, chest and abdomen revealed no abnormality. Lumbar puncture disclosed a clear, colorless fluid with an initial pressure of 110 mm. water, contained no cells, had a total protein of 37 mg. per 100 cc., negative Davies-Hinton and Wassermann tests, and the gold-sol curve was flat. Liver function tests disclosed the following: Cephalin flocculation: + (technique of Hanger¹⁵ normal response + to ++), prothrombin time (according to the method of Quick²²) 100%; icteric index: 3-4; serum bilirubin, prompt, direct 0.06 mg. %, total 0.36 mg. %; sulfobromophthalein excretion tests (by the method of White *et al.*²³) with 5 mg./Kg. wt. showed no dye

after 40 minutes; serum total protein was 6.88 gm. % with an A/G ratio of 4.3/2.5; blood CO₂ of 47%; thymol turbidity 2.23 cc. BaSO₄ (normal variation 0 to 1.68 cc.²¹); thymol flocculation (according to the method used by Neefe²⁶), 3 + (normal values 0 to +, exceptionally ++), and a blood urea 22 mg. %.

A month later, in April 1947, the serum total protein was 7.2 gm. %, and the cephalin flocculation was reported as 1 +. Two months later, on May 25, 1947, the serum total protein was 5.88 gm. %, while the cephalin flocculation was still 1 +, and the N.P.N. was 32 mg. %. The blood amino-nitrogen was slightly raised. During the patient's hospital stay a punch-biopsy of the liver was performed by Dr. Irving Brick. The specimens of liver tissue thus obtained were adequate, and histologic examination of the sections by the Mallory Institute of Pathology revealed no evidence of cirrhosis (Fig. 4). Dr. Parker kindly gave us the following critical evaluation of the sections: "There is great variation in the size of the liver cells. Some are much larger than normal. The cytoplasm of all the liver cells tends to be clear and contains numerous yellow-brown pigment granules. This pigment is not hemosiderin and is not acid-fast. The nuclei of the larger cells are abnormally large and sometimes are vacuolated. The lobular arrangement is somewhat distorted. There is no definite increase of the connective tissue in the portal areas which are infiltrated with an occasional lymphocyte and eosinophil."

Studies on the Urine. Concentration and dilution tests showed that the patient could concentrate urine to 1028 and dilute it to 1006. There was never any albumen, sugar, or acetone in the urine. Repeated examinations of the sediment were always negative. P.S.P. tests done in April 1947 and repeated in May 1947 showed 90% excretion of the dye at the end of 90 minutes with 35% excretion occurring within the first 15 minutes after injection.

Twenty-four-hour urine specimens were collected daily, the total volume was measured, then aliquots were taken for (a) determination of amino-nitrogen by the Soerensen Formol Titration, (b) amino-nitrogen determinations by the Van Slyke Ninhydrin method, (c) small aliquots used for the separation and identification of alanine, glutamic

and aspartic acids. Aliquots that could not be immediately used were frozen solid until a more opportune moment.

Total Daily Amino-nitrogen Excretion. The patient was found to excrete abnormally high levels of amino-nitrogen in the urine,

being made the blood N.P.N. varied between 32 and 36 mg. %, while the blood urea was recorded as 22 mg. %. The Formol titration was carried out according to Soerensen with the end-point at pH:9 on parallel samples. The blood amino-nitrogen titration was car-

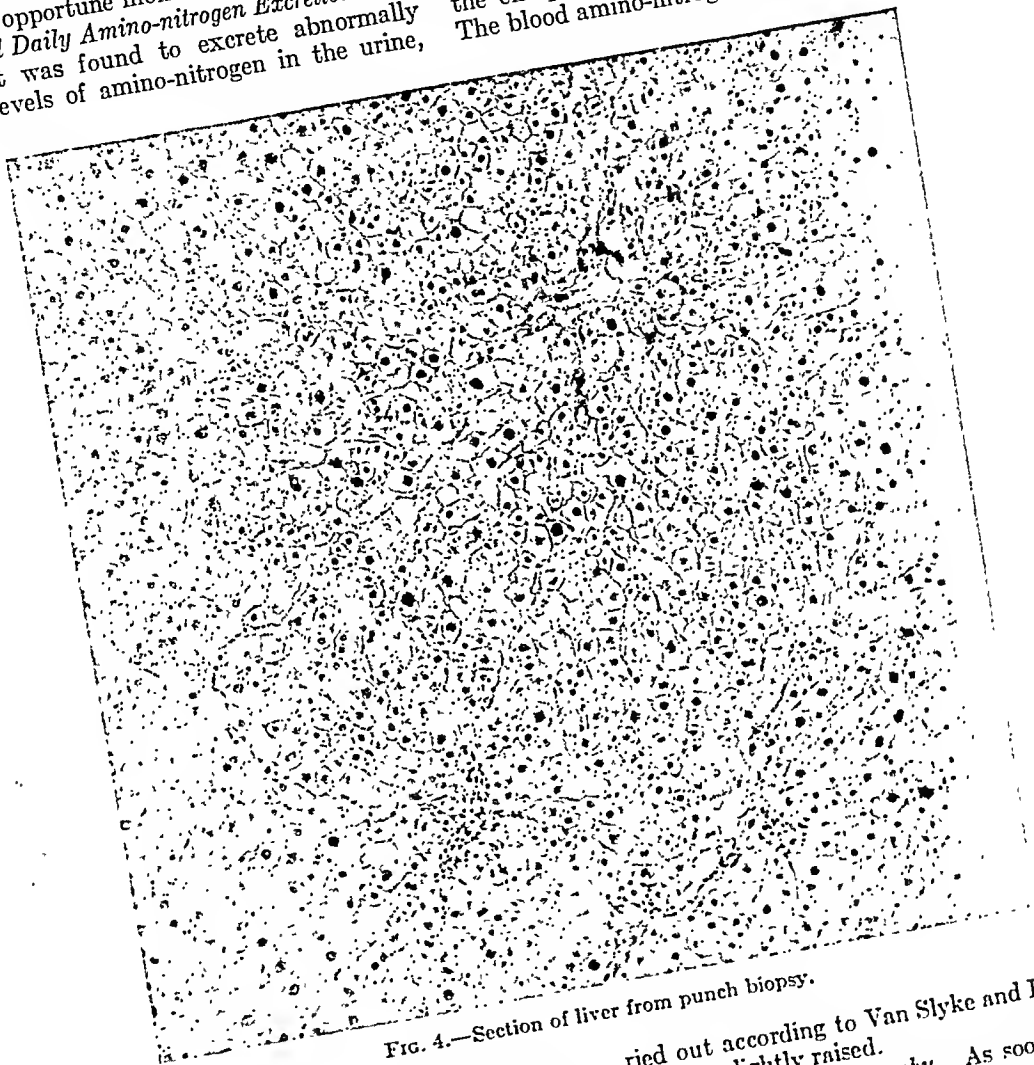


FIG. 4.—Section of liver from punch biopsy.

the total amounts varying between 800 mg. to 1500 mg. per 24 hours on a high protein diet (normal 100 to 200 mg. daily). The total amino-nitrogen was determined by Formol titration by one of us (L.U.). We are indebted to Dr. C. Davidson and associates of the Thorndike Memorial Laboratories for occasional Van Slyke Ninhydrin determinations. The results thus obtained are shown in Table 1. Putting the patient on a low protein diet (15 to 20 gm. daily) resulted in a slight reduction of the total amino-nitrogen excreted. Throughout the time during which these determinations were

ried out according to Van Slyke and Kirk^{31a} and was slightly raised.

Partition Chromatography. As soon as it was ascertained that the patient was excreting abnormally large amounts of amino acids, it became necessary to know whether the amino-nitrogen excreted belonged to a few amino acids like leucine and tyrosine, or whether most of the amino acids usually circulating in the blood were proportionally represented. For this purpose the paper partition chromatography first described by Consden *et al.*⁷ and later simplified by Dent⁹ was used. The chromatograms thus obtained

indicated that there were at least 10 to 12 different amino acids present, with the chromatogram spectrum extending all the way from the band of aspartic acid (with an R_F :0.12) to arginine and histidine with R_F values of 0.85 and 0.70 respectively. Repetition of these chromatograms after the 0.02 ml. urine sample had been appropriately diluted confirmed the observation that none of these amino acids was present in excess over the others. This seemed to exclude the possibility of the preponderance of any single amino acid in the urine of the patient.

gen sulfide. After the precipitated Cu was filtered off, aliquots of the filtrates of each fraction was taken for Nesslerization. Determinations on these samples gave a glutamic acid value of 42 mg. % and aspartic acid of 14 mg. %. Aspartic acid was further chemically identified by forming the benzoyl salt and comparing its melting point with synthetic benzoyl-aspartate:

	Melting point
Benzoyl compound from urine	179°-180° C.
Synthetic benzoyl-aspartate	179°-180° C.*

* Uncorrected.

TABLE 1

Soerensen formol titration			Ninhydrin-CO ₂ method mg. amino-N per 24 hrs.	Diet
Blood amino-N (mg.%)	Mg. amino-N per ml. urine	Mg. amino-N per 24 hrs. urinary excretion		
5.52	0 644	837	790	High protein
	0 56	896	923	"
	0 728	1237	..	"
	0 714	1249	..	"
	0 392	860	..	"
6.33	0 57	1534	..	"
	0 46	1246	..	"
	0 84	1558	..	"
	0 36	846	..	Low protein
	0.28	804	..	"
	580	"
	0.48	1440	..	High protein
	0.50	1275	..	"
	0.46	966	..	"
	0.52	988	..	"
	0.42	1120	..	"

Separation and Identification of Alanine, Glutamic and Aspartic Acids. Two hundred ml. of urine from a 24-hour specimen containing a total of 1535 mg. amino-nitrogen was reduced to 50 ml. by distilling *in vacuo*. To this was added barium hydroxide in powder form until the urine became alkaline. At this stage the sulfates were precipitated and filtered off. The Ba-salts of glutamic and aspartic acid were precipitated from the filtrate with 5 times the volume of ethanol (Foreman method). The precipitate was centrifuged off and redissolved in 10 ml. water. The Ba-ion was removed by dropwise addition of dilute sulfuric acid. The solution was then boiled for 15 minutes with 1500 mg. copper carbonate and then taken to dryness on a water bath. From the mixture of Cu-salts of aspartic and glutamic acids, the glutamic acid salt was separated by extracting the dry residue with water, the Cu-glutamate being water-soluble while the Cu-aspartate is water-insoluble. The copper was removed from both fractions with hydro-

Alanine was isolated from the same urine, after the Ba-fraction had been removed, by precipitating it according to Bergmann⁴ with dioxalopyridic acid. After this had been separated, the p-toluo-sulfonyl derivative of alanine was formed following the method of Bergmann and Niemann.⁵ The alanine thus estimated as the toluo-sulfonyl derivative gave a value of 102 mg. %. From this p-toluo-sulfonyl-alanine the p-phenyl-phenacyl salt was formed for purposes of chemical identification. Comparison of melting points (uncorrected) shows:

	Melting point
p-Phenyl-phenacyl compound from urine	142°-143° C.
p-Phenyl-phenacyl-alanine	142°-143° C.
p-Phenyl-phenacyl bromide	125°-126° C.

This value given for alanine may be rather high because it has been found that tryptophane will also give a dioxalopyridate whose solubility is low, *i. e.* 3 mg. per ml. at 5° C., and hence the precipitated dioxalopyridate may also contain some tryptodhane salt.⁶

Of course, the final purity of the phenylphenacyl compound does not argue against this possibility. The values thus obtained confirm the observation that there is a general increase in the individual amino acid fractions of the urine.

Discussion. The family reported in this paper present the pseudosclerotic type of hepato-lenticular degeneration which we have found to be more common than is generally believed. The peculiar tremor of cerebellar type has been described in some detail to facilitate its more general recognition. The Kayser-Fleischer ring of corneal pigmentation is its sure identification. The late development and very slow course of pseudosclerosis make it particularly appropriate for studies of metabolic dysfunction in hepato-lenticular degeneration. Such studies in the patient with the mildest form of the disease under our observation have revealed a gross aminoaciduria in the absence of demonstrable impairment of hepatic or renal function. The absence of low renal threshold for other substances excludes the Fanconi syndrome which is a nephrotic nephritis associated with albuminuria, renal glycosuria, hypophosphatemia, peptiduria and aminoaciduria due to "an inherent congenital defect of the tubular epithelium."

Although amino-aciduria is reported to be by no means uncommon in diseases affecting the parenchyma of the liver, the actual stage of liver disease in which the failure of de-amination of amino acids begins to occur and its relation to disturbances of the other functions of the liver are as yet unknown. One reason for this gap in our present knowledge may be the rarity of occasions in which investigators have been prompted to study quantitatively the amino acid excretion in the urine of patients showing minimal evidence of liver disease as indicated by the common liver function tests. Consequently, most of the literature on this subject reports the occurrence of abnormally large amounts of amino acids in the urine of patients whose hepatic function

had already shown gross and unmistakable disturbance. Undoubtedly the most striking instance of this is the amino-aciduria encountered in acute yellow atrophy (whatever the etiology) where urine amino-nitrogen levels of up to 40 mg. per 100 cc.²² and blood amino-nitrogen levels reaching 216 mg. per 100 cc.²⁷ have been reported. Less severe degrees of amino-aciduria are seen in subacute yellow atrophy,^{23,28} but in these cases it is quite transient and the major portion of the excreted amino-nitrogen can be directly ascribed to tyrosine. Deriving credence from these well-known observations, amino-aciduria has been generally considered as a manifestation of severe liver disease rapidly approaching the terminal phase of liver failure. True enough, at this stage of the picture, when the blood N.P.N. is rapidly rising and the blood urea level falls, the blood α -amino-nitrogen level is quite high and the excess amino acids are naturally poured out by the kidney. Yet the fact that the normal adult excretes about 100 to 200 mg. amino-nitrogen daily in his urine^{23,29} would indicate that the kidney will excrete amino acids even with a normal blood amino-nitrogen level. The lack of data on the tubular maximal resorption (Tm) of amino acids in the normal human kidney renders a correct appraisal and explanation of this phenomenon beyond our means at the present time. Recent renal clearance estimation of amino acids on dogs⁴⁰ are certainly not in accord with observed facts in normal humans, since the normal adult human excretes about 15 mg. arginine daily,¹⁶ and normal urine will give a strong Kappeller-Adler reaction for histidine, whereas in dogs, even with plasma levels of up to 10 to 50 times that of the post-absorptive state, there was no evidence that the maximal rate of tubular reabsorption for histidine had been reached, while the Tm for arginine was estimated as 11 mg. per minute. Hence it would appear that amino-aciduria in humans is not incompatible with the absence of concomitant hyperamino-acidemia, and an in-

crease in the former might well take place without a corresponding reflection in the latter. This supposition finds support in the case of hepato-lenticular degeneration reported here.

Conjectures concerning the cause of the amino-aciduria lead to the consideration of several possible explanations. One of these may be that failure of deamination might be by far the earliest hint of hepatic disease in hepato-lenticular degeneration. Certainly the presence of marked amino-aciduria with minimal impairment by liver function tests, as presented in our case, would support this hypothesis. Another and more attractive explanation would be provided by the assumption that Wilson's disease presents a basic fundamental defect in the metabolism of amino acids. The amino acids that cannot be used by a defective enzymatic system are excreted by the kidney, thus giving rise to a deficiency of amino acids essential for the maintenance of the functional and structural integrity of the liver and the basal ganglia of the brain. The detection of severe amino-aciduria without, apparently, any involvement of the liver severe enough to explain this phenomenon, would also support this second hypothesis.

Amino acid excretion studies done on patients who have already manifest hepatic dysfunction certainly are of little help in elucidating the cause of the amino-aciduria, since at that stage the liver itself is so severely affected that the amino-aciduria may directly be ascribed to the liver disease. This point was well-illustrated when we found the opportunity to reexamine a case previously studied by Homburger and Kozol (their Case 3).¹⁷ This patient had been steadily deteriorating since her evaluation in 1944 and 1946. The tremor has increased in severity, being markedly accentuated by any purposeful movement. It affected the upper extremities more than the lower, and the distal parts of the limb more than the proximal. Emotional instability was now conspicuous; the patient would laugh and cry on the slightest stimulus, and often her

features would shape themselves into a silly grin without mirth or affect. Memory and intellectual functions were also impaired. Judgment was poor and she was often found to indulge in bizarre behavior. The whole picture was consistent with progressive organic mental deterioration. Neurological findings were essentially the same as on previous admissions except for the presence now of bilateral extensor plantar (Babinski) responses. Liver function tests done a year after her previous study by Homburger and Kozol gave the following data: Cephalin flocculation +++ (previously + to ++++); icteric index 10 to 12; (previously 5); prothrombin time 72 % (previously 100 %); thymol flocculation 0 (normal: 0), thymol turbidity 0.72 (normal: 1.68); B.S.P.: 12 % retention of dye after 30 minutes (trace to 10 % after 15 minutes). The data reported by Homburger and Kozol are shown in brackets. The comparison shows distinct progression of her liver disease. Amino-nitrogen levels done on her 24-hour urine showed a daily out-put between 580 mg. and 690 mg. amino-nitrogen, but these levels were taken while she was dehydrated and refused to increase her fluid intake. As it is known, amino-acid out-put is also dependent on the total fluid excreted² and hence these values may well represent the minimal excretion levels. Thus, although this patient also showed amino-aciduria, this could be directly ascribable to her hepatic involvement.

The gross amino-aciduria in the presence of minimal liver disease in the case reported in this paper thus points to a very remarkable problem. This feature directs attention to the possible similarity of the condition with other well-known maladies associated with congenital defects of metabolism. Diseases like congenital cystonuria, alkaptonuria (homogentisinuria) and phenylketonuria, which are specific for certain metabolic systems, are also linked to hereditary and familial factors. Our finding strongly suggests that hepato-lenticular degeneration might justifiably be compared with congenital dis-

eases of metabolism. It is hoped that a larger family suffering from the disease may be found and the questions of whether the amino-aciduria exists from infancy could then be put to test. If such proves to be the case the whole mechanism of familial and hereditary nervous diseases which appear long after birth will be revealed in a new light. The conception of "abiotrophy" or premature aging of nerve cells finds little support in modern pathology. Damage to nervous structure resulting from the cumulative effects of inherent metabolic defects may well underlie such diseases as Huntington's chorea, presenile dementias, and other obscure syndromes.

The wide-spread use of intravenous alimentation with amino acids during World War II has shown that hyperamino-aciduria is well tolerated by the normal or undernourished individual, and that hyperamino-acidemia over a period of several weeks will not cause any neurologic disturbance. Thus, the possible affection of the basal ganglia by a chronic but very minimal hyperamino-acidemia due to faulty metabolism in the liver appears very unlikely.

Ever since Wilson's original description of the disease, investigators have found difficulty in demonstrating the hepatic damage in this disease by the usual liver function tests. Although claims have been advanced regarding the efficacy of the Serum Colloidal Gold reaction, this too is often as unreliable as the others. The Cephalin flocculation test has been found to be positive when other tests were negative. But such studies were made only

when the disease was already in an advanced stage. The studies reported here indicate that the presence of non-specific amino-aciduria, without demonstrable kidney or liver disease may well serve as a diagnostic criterion in hepato-lenticular degeneration at a stage where other tests give negative or doubtful indication. We have found only 2 references to tests for urinary amino acids in hepato-lenticular degeneration by others. Siemerling and Oloff³¹ report a slight increase in a patient whose liver was greatly enlarged. Lüthy²⁴ mentions that the ninhydrin reaction of the urine was negative in his first very chronic case, when other tests were also negative.

The total amino-nitrogen content of the 24-hour urine can be determined either by formol titration according to Soerensen or by the Van Slyke Ninhydrin-CO₂ method. Although the latter carries greater accuracy in α -amino-nitrogen determinations done on blood samples, the former has been found to be quite satisfactory in determinations done on the urine. Formol titration further possesses the advantage of being a simple procedure that can be carried out without complicated apparatus. The amount of urinary amino-nitrogen usually present renders the margin of error attached to this method a negligible factor.

Conclusions. One of 2 brothers suffering from the chronic pseudosclerotic form of hepato-lenticular degeneration was found to have a severe and persistent amino-aciduria. There was no evidence of renal disease. There was neither clinical nor laboratory evidence of hepatic cirrhosis. The implications of the amino-aciduria are discussed.

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DICUMAROL THERAPY IN ACUTE CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION

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IN 1938 Solandt and Best¹⁰ used heparin in the management of experimental coronary thrombosis. Those experiments paved the way for the application of anticoagulant therapy in human coronary artery thrombosis. Only during the past 4 years has the method been employed clinically, during which time both dicumarol and heparin have been on trial in the treatment of acute coronary occlusion with myocardial infarction. The rationale of anticoagulant therapy has been based on sound pharmacologic principles. These agents are used: (1) to prevent the formation of mural thrombi in the cardiac chambers; (2) to prevent the extension of a thrombus from its point of origin; (3) to prevent the formation of thrombi in peripheral vessels from which disturbing thrombo-emboli could propagate.

That acute coronary occlusion was accompanied by frequent thrombo-embolic phenomena has been long recognized. Wolff and White¹¹ have stated that a mural thrombus almost always occurs in patients who have suffered myocardial infarction, even though thrombi were found in only 30% of their postmortem material. Levine and Brown⁴ noted 83% mural thrombi in their fatal cases. In a clinical and pathologic study, Meakins and Eakin³ recorded 17% venous thrombosis, 42% pulmonary embolism, and 50% mural thrombi. In 300 infarctions, Bean¹ found 9% with pulmonary and 34% with systemic emboli, while 47% showed evidence of mural thrombi. In his group all of the pulmonary emboli and 15% of the systemic emboli were clinically detectable.

Conner and Holt³ recorded clinical systemic embolic complications in 10% of 287 patients, of whom 7% had pulmonary emboli. More recently Nay and Barnes⁶ have reported thrombo-embolic complications in 37% of 100 cases convalescing from acute coronary occlusion—15% complicated by a second infarction, 14% by pulmonary emboli, 8% by cerebrovascular occlusion, 7% by thrombophlebitis, and 4% by peripheral arterial occlusion.

According to these necropsy studies, mural thrombi were found in the majority of myocardial infarctions. Emboli from the left heart were noted in variable percentages in the spleen, kidney, brain, mesenteric and extremity vessels, while those from the right heart necessarily lodged in the pulmonary tree.

With the advent of the anticoagulant era, Peters, Guyther and Brambel⁹ treated 60 instances of acute myocardial infarction with dicumarol with 2% vascular complications and 4% mortality. Also Nichol and Page⁷ treating 44 patients, and Wright¹² in his report of 76 acute occlusions treated with this anticoagulant, indicated that both the incidence of thrombo-embolic complications and the mortality rate were appreciably lowered. Parker and Barker³ likewise observed 50 patients, 40 of whom were treated solely by dicumarol and 10 by a combined dicumarol-heparin program. They noted vascular complications in 4% with 10% mortality.

Material and Methods. This communication records our experience with 71 consecutive admissions. The diagnosis was substantiated by history, clinical signs and

symptoms, laboratory data and the development of electrocardiographic patterns of acute anterior, posterior, or lateral wall infarction, and/or a combination of these. Three who died within 48 hours of admission are omitted from the statistical data. Known coronary occlusion had occurred in 2 patients, one 9 months and the other 16 months previously.

Anticoagulant therapy consisted solely of dicumarol. In addition, all patients received papaverine hydrochloride during the entire period of hospitalization. Oxygen by catheter, and morphine intravenously or subcutaneously, were routine procedures during the first 3 days and administered as necessary thereafter. Sodium restriction and leg exercises completed the régime.

Prothrombin times were performed daily by a modification of Quick's method, using Difco's thromboplastin from rabbit brain. In control readings, prothrombin times have consistently varied between 12 and 15 seconds. An initial 300 mg. of dicumarol were administered after the prothrombin time had been determined, and 200 mg. were given routinely on the 2nd day. It was our purpose to maintain the prothrombin level between 30 and 45 seconds by the administration of 100 or 200 mg. daily for 4 weeks. If and when the prothrombin time reached 35 seconds, dicumarol was omitted that day.

OBSERVATIONS. Table 1 shows the distribution of these patients according to age by decade, Table 2 according to sex and

race. Interestingly enough, 3 Chinese males in their 5th decade were treated during this study. Of the series, 44 (62%) were in the 5th and 6th decades. Serial electrocardiograms (Table 3) demonstrated that anterior and antero-lateral patterns barely exceeded the posterior lesions.

TABLE 3.—ELECTROCARDIOGRAPHIC LESION

Anterior occlusion	37
Posterior occlusion	31
Mixed type	3
Total	71

On 3 occasions gross hematuria occurred which was readily controlled by intravenous administration of 60 mg. of menadione bisulfite. This complication occurred during the 3rd week of therapy in 2 instances, so dicumarol was discontinued. It was resumed in the third patient without subsequent hemorrhage. Two instances of mild epistaxis were noted, but these patients were maintained continuously at therapeutic levels. Unexplained difficulty was encountered in the maintenance of the desired prothrombin time in 21 patients. In 10 of these, a lapse of 4 days occurred before a therapeutic range was attained. On 4 occasions prothrombin times increased beyond 60 seconds, uncomplicated by hemorrhage. One instance of elevated prothrombin time was demonstrated 6 days after the anticoagulant had been discontinued, though clinical evidence of hepatic or renal dysfunction was lacking. There were 6 patients in whom effective therapeutic control lapsed for a day or more without clinically detectable vascular mishap. An elderly male had an apparent extension of his infarction during the 3rd week of his illness when the prothrombin time was 39 seconds. Serial electrocardiograms gave evidence of a progression of the lesion, and the patient expired suddenly on the 20th hospital day. Whether there was an extension of the thrombus, or whether ischemic infarction without thrombosis occurred, could not be ascertained.

Thrombo-embolic complications were

TABLE 1.—DISTRIBUTION ACCORDING TO AGE

Age	No.
20-29	0
30-39	6
40-49	15
50-59	26
60-69	18
70-79	6
Total	71

TABLE 2.—DISTRIBUTION BY SEX AND RACE

Sex	No.
Male	65
Female	6
Total	71
White	67
Black	1
Yellow	3
Total	71

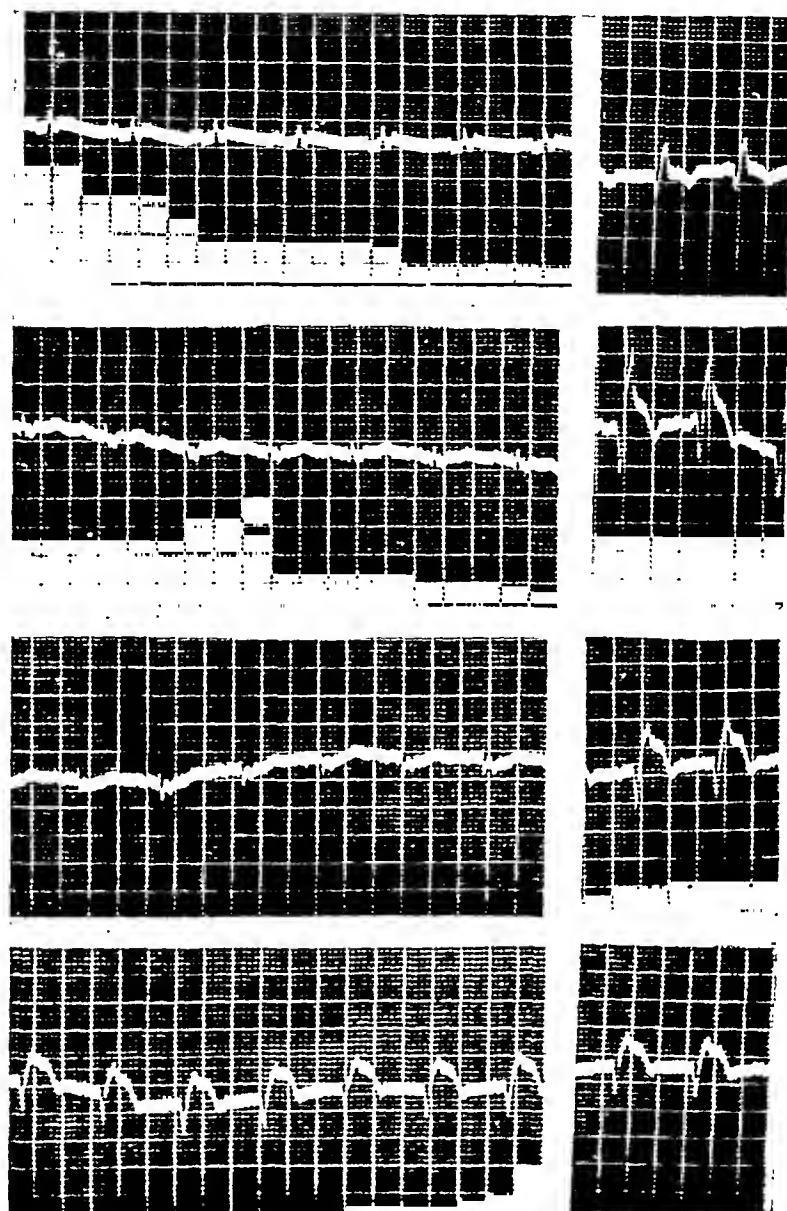


FIG. 1.—White male, age 65. Arteriosclerotic heart disease with antero-lateral myocardial infarction on the day prior to death. From above downward, on left, Leads I, II, III, IVF and on right CF₁, CF₂, CF₃, CF₄. The S—T segments were markedly shifted from onset.

notably infrequent. They were observed in 2 patients, 1 being the fatality previously described. The other was an elderly patient whose rhythm was totally irregular in whom a pulmonary embolus occurred on the 6th day, when the prothrombin time was 30 seconds. Necropsy revealed the pulmonary embolus, but evidence of mural thrombi was lacking.

TABLE 4.—CAUSE, AGE AND DAY OF DEATH OF 9 FATAL CASES

Cause	Age	Day
Heart failure	50	10
	55	27
	58	10
	61	10
	65	4
	67	4
Ruptured ventricle	40	3
Pulmonary embolus	75	6
Extension of infarction	67	20

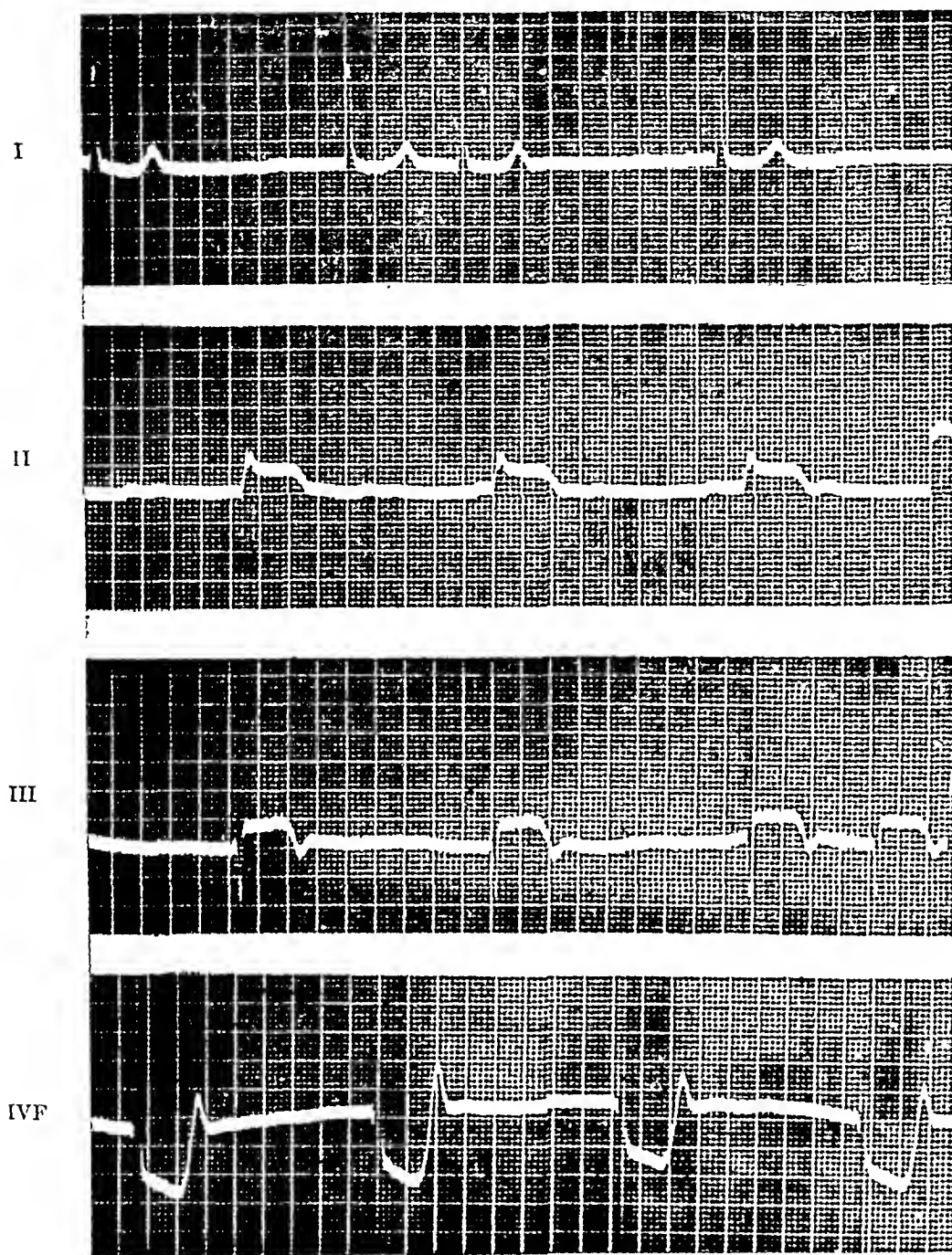


FIG. 2.—White male, age 67. Arteriosclerotic heart disease with posterior myocardial infarction. Complete heart block and persistent S-T shift are evident on the day of death.

Nine deaths in this group gave a mortality incidence of 12.7% (Table 4). Rupture of the heart occurred on the 3rd day in a patient 40 years of age. This lesion involved a large area of the septum, following a thrombosis of the right coronary artery. Extension of the infarction was the cause of death in 1 instance, and pulmonary embolus was a contributory

cause in another. The remaining 6 patients died of cardiac failure. In 3 of the latter, marked shifting of the S-T segments persisted until death (Fig. 1). Complete heart block, associated with a posterior lesion, occurred in an elderly male who expired on the 10th day (Fig. 2). In these patients who came to necropsy, no mural thrombi were found.

Comment. From observations made on 71 patients no effort has been made to compile statistical data. Though certain features were undesirable, it seems that this pharmacologic approach is sound. The appearance of hemorrhagic complications, especially hematuria, was unpleasant; but we can emphatically state that serious harm due to the drug did not occur. This sole hazard was controlled by menadione bisulfite. On the other hand, in 10 patients 4 days elapsed before the therapeutic level was reached. Despite this fact, evidence of thrombo-embolic complications was not noted in this group. Perhaps the most useful purpose served by dicumarol therapy is prevention of thrombus formation in pelvic

and leg vessels, as well as the septal and mural areas. The conspicuous low incidence of thrombo-embolic phenomena would seem to justify this conclusion.

Summary and Conclusions. 1. Dicumarol has been used as the sole anticoagulant in the management of 71 patients with myocardial infarction following acute coronary occlusion.

2. This therapeutic approach is sound.

3. Daily prothrombin determination is mandatory for successful therapy.

4. Hemorrhagic complications were infrequent and readily controlled.

5. Due to the low incidence of thrombo-embolic phenomena a less stormy convalescent period was insured, justifying the continued use of this form of therapy.

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FURTHER STUDIES ON THE ANTICOAGULANTS

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This report embodies a continuation of studies on dicumarol and heparin initiated at Lenox Hill Hospital in 1943. Since that time these anticoagulants have been under constant observation at this institution. They have been used both for the prevention and the treatment of thrombotic conditions. Favorable results have been described in previous communications.^{8,9,13}

The present series of cases of approximately 300 patients can be divided into 4 main groups: (1) postoperative cases treated prophylactically with anticoagulants to prevent thrombotic conditions; (2) patients with active venous thrombosis; (3) acute embolic episodes, usually pulmonary; and (4) cases of coronary thrombosis.

The general technique of performing the prothrombin tests has been previously described in detail. The prothrombin times were reported in seconds and referred to normal controls. The normal values ranged from 12 to 15 seconds. The conversion of prothrombin times to values designated as percentage of normal concentration may readily be performed by referring to a normal control curve of prothrombin times of serially diluted plasma.^{1,3,7}

While it is felt that such a conversion is very useful in many instances, we found it to be simpler, especially for the laboratory, and just as satisfactory in managing patients on dicumarol therapy, to use the direct time. Furthermore, in preparing the normal curve, in the process of diluting with plasma another factor in the clotting mechanism, namely

fibrinogen, is reduced as a result, prothrombin times done on dilute plasma will not reflect the true prothrombin level of the blood, unless fibrinogen is added in the dilution process.^{1,3,7}

DRUGS AND METHODS OF TREATMENT. There have been some changes lately in the methods of administering the anticoagulants so that it is best to describe the technique in detail.

Heparin. This substance can now be given in 3 different ways, all parenteral of course: (a) A 10 cc. vial of heparin containing 10 mg. is added to each 500 cc. of saline and is administered as a continuous intravenous infusion at the rate of 30 drops a minute at the onset. Coagulation times are carefully done every 4 hours by the Lee-White method, the object being to prolong the coagulation time to 3 times normal. This can be fairly steadily maintained, providing close supervision by the nursing staff is available. The main objection to this form of administration lies in the precise control of the rate of flow that is required and this necessitates very frequent observations. Variations in the rate of flow such as can occur with different positions of the arm may result in extreme variations in the coagulation time.

(b) Heparin (50 to 100 mg.) is injected intravenously undiluted every 4 to 6 hours. One difficulty in this form of administration is the inconvenience of the multiple injections. Jorpes⁹ who has had considerable experience with this method considers it safe enough to dispense with the usual check of the coagulation time.

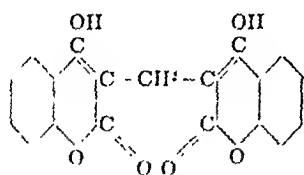
(c) Heparin, 200 to 400 mg. in Pitkin-

menstruum, is given in the deep subcutaneous tissues at 48 hour intervals. Loewe⁵ has recently reported on this method.

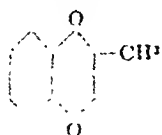
Naturally frequent coagulation times should be done to check the effectiveness of the latter 2 methods of administration. The expense of both of these is considerably greater than dicumarol therapy and hence heparin therapy is merely used until dicumarol has taken effect.

If hemorrhage should occur, heparin of course is promptly discontinued and the heparin effect will be lost in several hours. If the severity of the bleeding necessitates prompt treatment the administration of whole blood is indicated.

Dicumarol. Dicumarol is a tasteless, odorless, white powder available in 100 and 50 mg. capsules. Its chemical structure is 3,3'-methylenebis-(4-hydroxycoumarin) and, as had been frequently noted yet commonly overlooked, its structure is very similar to vitamin K. Thus one of the synthetic compounds possessing high vitamin K activity is 2-methyl, 1,4-naphthoquinone, the structural formula of which resembles half of the dicumarol formula.



3,3'-methylenebis-(4-hydroxycoumarin)



2-methyl-1,4-naphthoquinone

FIG. 1. Structure of dicumarol and a synthetic vitamin K

Through a process of biologic antagonism¹² the mechanism of action of dicumarol is postulated as one of interference in the production of prothrombin by the liver cells at some point where the normal mechanism utilizes vitamin K. A mass action can explain the fact that vitamin K

administered intravenously in high dosage (60 to 120 mg. of water-soluble vitamin K) can return toward normal a prothrombin time that has been prolonged by dicumarol.

Before administration of the drug a prothrombin determination is done to find the patient's normal blood level. This is necessary to avoid treating cases where the production of prothrombin is already impaired, such as with diffuse liver damage, for in these patients small doses give excessive effects.¹¹ It is important to note the state of the urinary system, for dicumarol is excreted by the kidney. With primary renal retention as well as with diminished renal blood flow, dicumarol is retained and unexpectedly prolonged prothrombin times will result.¹⁰

After the preliminary prothrombin time has been established, 300 mg. of dicumarol are given. Daily prothrombin levels are done and until the desired range is reached 200 mg. are given each day. The object is to prolong the prothrombin time to twice its normal value. In other words, if the normal control is 14 seconds, the therapeutic range would be above 28 seconds. Ideally it would be desirable to keep a patient at just above this level, but practically this is not often possible. Hence, therapy has to be guided mainly by the minimal level desired and in an effort to keep above this, prothrombin levels of 3 or 4 times normal are frequently encountered without any particular risk.

Naturally every patient reacts differently to drugs and it is necessary to adjust subsequent doses individually. Once the therapeutic level has been reached no further drug need be given until the prothrombin time has dropped below or is rapidly decreasing toward this level. Thus with a control prothrombin time of 14 seconds, and that of the patient 35 seconds, no drug would be given if the latter represented a rapidly increasing prothrombin time. On the other hand an additional 100 mg. of drug would be administered if this represented a rapidly falling prothrombin time. This merely represents an effort to take into account the delayed

effect of dicumarol, for only by doing so can one prevent the drop out of the effective range which can readily occur and be quite disastrous. One of our patients with phlebitis migrans illustrates this last point very well, for over a 5 week period every time his prothrombin time dropped below about 28 to 30 seconds (with a control of 12 to 14 seconds) he developed a new phlebitis.

If inadvertently bleeding of a serious degree occurs, a transfusion of fresh blood plus 60 mg. of water-soluble vitamin K intravenously will raise the prothrombin level promptly. The transfusion gives a rapid effect, whereas the vitamin K effect is not as prompt but is manifested only after some hours. Vitamin K administration may be repeated several times if the circumstances indicate.

The above is merely the general technique of administering dicumarol. There are many variations and each person must be judged as an individual as with all other drugs. There are some hyperreactors in whom the administration of 300 mg. the first day, followed by 200 mg. the second, will send the prothrombin time up to 70 or 80 seconds over the next 5 days, and there are resistant cases who need 200 mg. daily to keep them in the therapeutic range.

The combined use of heparin and dicumarol is frequently indicated, for such is the ideal treatment when an immediate anticoagulant effect is indicated in a case that will also require prolonged effect as well. There may be some confusion in these cases in estimating the dicumarol time and the readings are not solely due to dicumarol as long as the heparin is given. Therefore it is best to give 300 mg. of dicumarol the 1st day and 200 mg. the 2nd, even if the prothrombin time is unduly elevated, as this is probably an additional heparin effect. If the dicumarol is withheld the patient will drop back out of the therapeutic range when the heparin is stopped and then be in danger of embolization.

The heparin is usually discontinued at

36 to 48 hours so that thereafter the prothrombin times can again be relied upon as indicating dicumarol effect.

We will now proceed with discussion of the different groups of cases and the therapeutic variations indicated in each group:

1. THE POSTOPERATIVE PROPHYLACTIC CASES. There were about 200 of these and at least 50% were after pelvic operative procedures in women. The others were after the usual type of operations and there were also some postpartum cases in whom there had been a previous history of phlebitis. In none of these cases did a phlebitis or pulmonary embolism develop.

The treatment in this group of cases was by means of dicumarol. It was started 2 to 4 days postoperatively and kept up until the patient was ambulatory (about 7 to 10 days). In ordinary cases the drug can be started on the 2nd postoperative day, but after operations involving a particularly vascular field such as gastric resection, prostatic operations, cholecystectomy and postpartum cases, it is better to wait 4 days before administering the drug.

The only hemorrhagic manifestation in this group were 2 wound hematoma and they occurred when the prothrombin times were not too unusually high. Also occasional episodes of minimal vaginal bleeding complicated pelvic cases but were not of sufficient degree to interrupt dicumarol therapy. We have found dicumarol a safe drug to give with little danger of significant bleeding. Naturally, the prothrombin times were watched carefully; in some cases they rose to very high levels but no bleeding occurred.

The results in this group have been most satisfactory. From our own experience both past and present as well as that of other investigators,² it is now possible by prophylactic use of dicumarol practically to guarantee the prevention of postoperative thromboses. As to whether this prophylactic treatment should be used after all surgical procedures or only after those in which thromboses are more likely, as in pelvic operations, is a moot question,

Thromboses and pulmonary emboli have been known to occur after any operation and in persons of all ages.

Dicumarol treatment is safe, the only inconvenience to the patient being the daily venepuncture entailed in taking the blood for the prothrombin determinations. This technical procedure and the necessary laboratory work in doing the tests are a small price to pay to ward off the uncertainty and cataclysmic consequences of a postoperative embolism.

2. ACUTE EMBOLIZATION. There were 30 cases of acute embolization treated; 26 were pulmonary, 3 cerebral and 1 peripheral. Most of the pulmonary cases were typical, occurring without warning between the 7th and 14th postoperative day. In some there was a demonstrable antecedent phlebothrombosis, but in the majority there were no signs or symptoms pointing to a causative thrombosis. Prophylactic venous ligation would have been useless in many cases as the thrombotic focus in these instances was likely pelvic in origin, especially in view of the fact that most of the pulmonary emboli occurred after pelvic operations or postpartum.

The typical history of acute pulmonary embolism was sudden pain in the chest, rapid shallow difficult breathing, tachycardia and cyanosis. There was often hemoptysis and Roentgen ray examination in classical cases showed an area of infarction. This Roentgen ray evidence was not always present early in the disease and in some cases could not be demonstrated at all.

Combined heparin and dicumarol therapy is employed in these cases because being most urgent it is important to get an immediate anticoagulant effect. Therefore heparin is injected as soon as possible. Dicumarol is started at the same time and as soon as the prothrombin time indicates that the patient is under its influence the heparin can be stopped. This is usually in 36 to 48 hours. To avoid the effect of heparin on the prothrombin time, blood for this determination should be

taken after the coagulation time has been allowed to drop toward normal.

Other treatment for pulmonary embolism such as oxygen, penicillin and papaverine for sedation are used at the same time. All of our cases of embolization recovered except 2 which will be described in detail. One other case had a subsequent non-fatal embolism while on anticoagulant therapy. These 3 cases are summarized as follows:

Clinical Notes. CASE 1. A 60 year old male developed a pulmonary embolism, 18 days after a myocardial infarction. Under dicumarol he had no further emboli but suffered persistent pain in the right chest at the site of the embolus. Ten days later this area of infarction broke down into a pulmonary abscess with copious green purulent sputum. His temperature persisted high and he died 4 days later.

In this case it is worthy to note that relatively small amounts of dicumarol, without any additional drugs, caused his prothrombin time to rise to unusually high levels, reaching 85 seconds, and persisting there for days. We feel that the significant feature in his sensitivity to the drug was his impaired blood circulation with resultant diminished renal circulation and dicumarol retention.

CASE 20.—A 63 year old male had bronchiectasis, multiple migrating phlebitis and several embolic episodes. In this case it was necessary to keep the prothrombin time at comparatively high levels, 50 to 60 seconds, to prevent further phlebitis and emboli. However, in the 10 day period following the attainment of adequate levels an area of pulmonary infarction broke down into a large abscess and the patient died. At autopsy the pulmonary condition was confirmed and it was also found that he had a carcinoma of the pancreas. This may have been a factor in the production of multiple phlebitis.

CASE 27. A 37 year old female, 7 days postpartum had a severe pulmonary embolism on her 1st ambulatory day and within 24 hours she had another similar episode. At that point combined heparin and dicuma-

arol treatment was started. Two days later vaginal bleeding which had never completely disappeared since the delivery became a bit more profuse due to the anticoagulant therapy, and some pituitary extract was given. It is impossible to say whether this is merely coincidental, but shortly after its administration another embolic episode of less severe degree occurred. Earlier she had shown signs of a minimal phlebitis in her left calf and on the possibility that this was the source instead of her pelvic veins, a superficial femoral ligation was performed, the vein revealing no thrombosis at the time of operation. At any rate, whatever the source she had no further complications.

The following case is also of interest.

CASE 24. A 64 year old female suffered from a peripheral arterial embolus involving the lower extremities. Dicumarol was given but amputation could not be avoided. At operation there was no excess bleeding despite the fact that the prothrombin time was twice normal.

This again illustrates that the fear of bleeding from the use of dicumarol is often exaggerated. Nevertheless, if surgery is contemplated in a patient under the influence of dicumarol it is best to inject 120 mg. vitamin K by vein a few hours preoperatively as a precautionary measure.

3. PHLEBITIS. There were 45 cases of thrombophlebitis, which included both deep and superficial phlebitis. For our purpose it is not necessary to separate the superficial from the deep cases as the therapy is usually similar. Twenty of the cases were postoperative patients who had received no prophylactic anticoagulant treatment. Of these 20 cases, 15 were women who had undergone pelvic operations or childbirth. This again emphasizes the increased tendency to thrombosis after pelvic surgery or parturition. The other 25 cases of phlebitis were associated with the usual well-known etiologic factors. A few are worthy of mention. Three were after trauma to the leg, one was after several infusions with protein hydroly-

sate, and another associated with a severe case of polycythemia, while another was in a young patient recovering from infectious mononucleosis.

We shall discuss one case in detail, a site is very unusual from various standpoints.

CASE 64. A 42 year old white male was admitted to the hospital with the diagnosis of a deep phlebitis of the left leg. Dicumarol was administered in the usual manner. During the next 5 weeks, every time the prothrombin level fell to below 30 seconds another vein became involved. This was evidently a case of thrombophlebitis migrans and as these are often associated with neoplasms, an effort was made to find such a focus. Chest Roentgen rays were taken and a biopsy of some slightly enlarged lymph nodes in the right side of the neck was done. A lesion was found in the lungs and the biopsy showed adenocarcinoma, primary site undetermined. Eventually the deep superficial veins of both legs, both arms, the right external jugular and the veins of the penis became involved. To prevent any further involvement it was decided to take the risk of keeping him at high levels. These averaged 80 seconds for about 6 weeks and during this period there was no further venous thrombosis. Then for a month at normal levels he had no further thrombosis. It is interesting to note that at the time of the right cervical biopsy the prothrombin time was 87 seconds with a control of 14 seconds, and yet there was no abnormal bleeding. The patient returned home and in 2 months died suddenly.

The treatment of phlebitis is by dicumarol rather than heparin as there is no necessity for urgency, except in a severe acute case. Additional measures that seemed of value² are papaverine, $\frac{1}{2}$ gr. every 4 hours for pain, a cradle, elevation of the leg, and continuous hot wet dressings. Under dicumarol the average case of phlebitis lasts about 7 days. As soon as the inflammation subsides and the temperature is normal, the patient is allowed out of bed. An ace bandage is worn for several weeks after recovery. If infection associated with the phlebitis is severe and the temperature persists, sulfonamides

and antibiotics can be used as indicated.

In none of our cases so treated were there any pulmonary emboli. The unfortunate thing about phlebitis is that once an entire vein becomes involved some residual edema often remains. By the prompt use of the anticoagulants, thrombosis can be restricted to just one segment of the vein and often the collateral circulation is sufficient to prevent lymphatic stasis.

4. CORONARY ARTERY DISEASE. There were 30 cases of coronary artery disease treated with dicummarol; 24 of these were typical coronary occlusions with myocardial infarction. Of these, 4 died; 2 of progressive failures, 1 after having shown clinical and electrocardiographic evidence of progressive myocardial damage, and 1 in what seemed to be an acute new coronary episode. No one, however, had either pulmonary or coronary insufficiency. It is interesting that 1 of these latter cases who had a long history of coronary insufficiency, manifested by anginal attacks and ECG evidence of myocardial damage, suffered what appeared to be clinically an acute coronary attack while on adequate dicummarol therapy. She died before ECG confirmation could be had and unfortunately postmortem examination was not permitted.

A few cases will be presented to illustrate salient points.

CASE 1. A 57 year old male was treated uneventfully with dicummarol for 5 weeks when he developed a sudden profuse hemorrhage from the lower bowel. The prothrombin time oddly enough had dropped to less than 30 seconds before the hemorrhage occurred, a level at which no other bleeding manifestations have been noted here. He was given a blood transfusion and 120 mg. "hykinone" and recovered uneventfully.

CASE 3. A 74 year old male developed what appeared to be a progressive coronary involvement while under adequate dicummarol therapy. The ECG suggested a new infarction when the prothrombin time was 40 seconds with a control of 13 seconds. With this new episode he went into failure which persisted until his death, several days

later. During this time the prothrombin times reached unexpectedly high levels, 75 seconds, with minimal dosage, whereas previously he had a fairly steady maintenance on normal dosage.

CASE 4. A 53 year old male was doing well under dicummarol when he developed a sudden recurrence of substernal distress, 25 days after his original coronary episode. He went into shock, became cyanotic and died. Autopsy was refused. This was probably another coronary episode, though a pulmonary infarction cannot be definitely excluded.

CASE 9. A 56 year old male who was a postoperative prostatectomy developed a typical coronary episode. He was started with 300 mg. dicummarol and then given another 300 mg. by mistake. One-half hour later he was treated by gastric lavage, but in spite of this his prothrombin time rose to 176 seconds, 3 days after the initial dose. He had no bleeding and responded promptly to 180 mg. of hykinone. Subsequently he was quite sensitive to dicummarol, but under careful management remained in good control. This case illustrates the fact that bleeding does not always occur even though the prothrombin time is very much prolonged.

Thus while this group is too small to present any definite conclusions, the impression given is that the main usefulness of anticoagulant therapy in coronary artery disease is in the prevention of embolization either from peripheral vein or cardiac mural thrombi. This conforms with the impressions of others.^{2,6} Although in most of the cases of coronary artery disease no further acute cardiac episodes occurred while under the influence of anticoagulants, it was nevertheless observed that a small proportion definitely had second episodes. This suggests that anticoagulants are unable to influence the further development of a coronary thrombosis where the degenerative artery disease is sufficiently advanced. Thus whereas the anticoagulants are in no way able to prevent acute coronary episodes they can nevertheless aid in prolonging the life of these patients, by the prevention of secondary embolization. This alone would make their use in cases

of coronary disease worthwhile. It has been our observation that some patients with coronary disease are unduly sensitive to dicumarol but this was only in cases complicated by quite marked cardiac failure. The majority of the cases manifested an acute coronary episode without any prolonged shock state and without any obvious degree of congestive failure, and these showed no unusual sensitivity to dicumarol. Presumably the increased sensitivity in cases of congestive failure is due to the decreased renal blood flow and secondary retention of dicumarol which is normally excreted by the kidneys.

Summary and Conclusion. From an analysis of our previous reported studies on anticoagulants dating back to 1943 and our present series of 300 cases we can summarize as follows: 1. Postoperative venous thrombosis and pulmonary embolism can definitely be prevented in all cases by the prophylactic use of anticoagulants.

2. The treatment of established thrombotic conditions by means of anticoagulants is effective and safe.

3. In coronary artery disease the main value of the anticoagulants is the prevention of complicating embolization.

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HAS METHIONINE A PROTEIN SPARING EFFECT IN ACUTE INFECTIOUS HEPATITIS?*

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Two basic actions of methionine have been established. By providing labile methyl groups, it acts as a lipotropic agent instrumental in the removal of fat from the liver^{10,15,16} and by supplying sulphhydryl groups, it aids in the detoxification of liver poisons.^{6,30} As a result of these activities, it has been ascribed a therapeutic effect in liver disease. There is well-established evidence that nutritional experimental cirrhosis or necrosis produced by low protein diet can be improved by treatment with methionine.^{15,18,26} Furthermore, protection against experimental liver injury has been provided by this substance.^{28,30} In human cirrhosis, methionine is of proven value, at least if the liver is large.^{5,13} In toxic hepatitis caused, for example, by carbon tetrachloride, methionine seems to be beneficial.^{4,11,12} Its therapeutic effect in infectious hepatitis of the viral type, however, is questionable.^{17,19,35}

It is extremely difficult to obtain information concerning the therapeutic effect of any procedure in viral hepatitis because of its erratic, unpredictable course. To answer this question, therefore, another approach, based on nutritional theories, may be taken. Methionine used either for lipotropic activity or provision of sulphhydryl groups is obviously not available for

protein synthesis. If patients with viral hepatitis were given protein in an amount to keep them just below nitrogen equilibrium, the addition of methionine would bring them into positive nitrogen balance. If significant amounts of methionine had been used for purposes other than protein formation, *i. e.*, methionine deficiency was present. Demonstration of methionine deficiency in infectious hepatitis would thus indicate a rationale for methionine therapy in this condition.

The rôle of methionine in protein metabolism has been thoroughly investigated. It was shown that methionine was a key amino acid in the regeneration of serum protein in adult dogs.²⁴ It has a protein sparing effect in dogs on a low protein diet^{2,7,27} or in burned rats on a normal diet.⁹ In man, however, either healthy²² or after operation³³ methionine supplementation did not significantly influence nitrogen balance. A recent extensive study⁸ established a difference between the human being and animals in methionine requirements as well for growth as for nitrogen balance. In 3 patients with pyloric obstruction, to whom casein hydrolysate was given intravenously, in 2 infants and in 10 volunteers who received the same preparation by mouth, the addition of

* Supported by a grant from the Biochemical Division of Interchemical Corporation, Union, New Jersey.

the methionine produced no significant changes in growth or the nitrogen requirements.

Material and Method. Four patients with moderately severe infectious hepatitis revealing the characteristic clinical symptoms and laboratory findings represented the material of this study. During the height of the disease they were transferred to a metabolic unit where they remained for 19 to 25 days.

hour samples; stool and urine were examined for nitrogen by a modified micro-Kjeldhal method.²⁰

The basic diet consisted of carbohydrate beverage, cereal of low nitrogen content, coffee, sugar and fruits. The total amount of nitrogen provided by this diet was below 500 mg. per day. For the individual patients the intake was kept constant during the entire experimental period. In the nitrogen balance calculation, it was not taken into

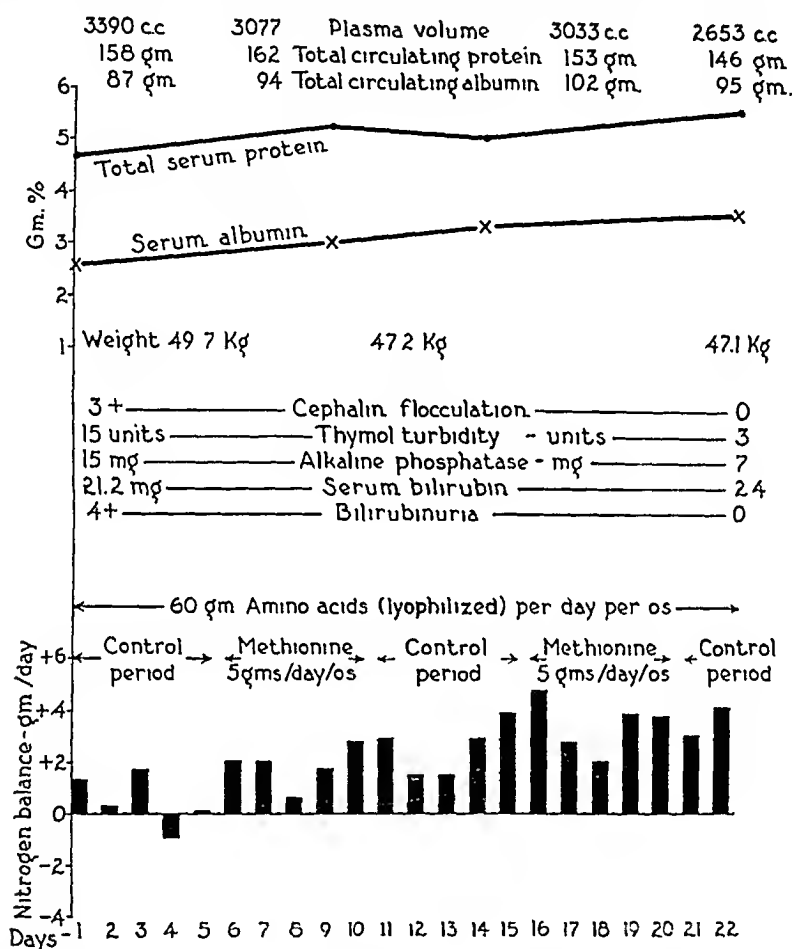


FIG. 1.—Results of studies in a 23 year old white male who entered the hospital after 1 week of prodromal symptoms (anorexia, nausea, vomiting, abdominal pains, and frequent stools) and 2 weeks of jaundice. The liver was 3 fingers below the right costal margin. Spleen was not felt. The experiments started 16 days after the outbreak of jaundice. The recovery was uneventful and the patient was discharged 10 days after the end of the experiment.

Various liver function tests were performed periodically. In addition to blood counts and urinalyses, plasma volume was determined according to the method of Gregerson.¹⁴ During their stay in the metabolic unit, they were under continuous supervision so as to guarantee reliable urine and stool collection. The urine was collected in 24

consideration. Further experimental details are given elsewhere.²¹

Practically the entire nitrogen requirements were provided by a modified protein hydrolysate.* The material was available as a dried powder in 750 cc. flasks and contained the essential amino acids in more than adequate amount. The ability of this prepa-

* Elamine Lyophilized, provided by Interchemical Corporation, Union, New Jersey.

ration to produce nitrogen balance, if given intravenously as main source of nitrogen, had been proven previously.²¹ In this experiment, it was administered orally in foods or drinks. Two patients received amounts which were definitely inadequate, namely, 0.5 gm. of amino acids per kg. body weight, and 2 received amounts approximately adequate, namely, 1.2 and 1.41 gm. per kg. body weight. During the experimental period, 5 gm. methionine† (or for comparison, as a matter of convenience, during 1 period, 5 gm. lysine‡) were given orally in 3 doses during the day. The experimental periods lasted 5 to 6 days and were preceded and followed by control periods of various lengths.

Results. The clinical condition of all 4 patients improved significantly during the experiment and the liver function tests returned to normal (Figs. 1, 2, 3, 4). The amounts of nitrogen given did not seem to influence this process of recovery. The nitrogen excretion revealed a tendency to decrease during the entire experiment. This resulted in a gradual approach of nitrogen equilibrium or even positive balance in the 3 patients in which there was marked negative nitrogen balance at the onset. In the 1 case, in which the nitrogen balance was positive already at the onset

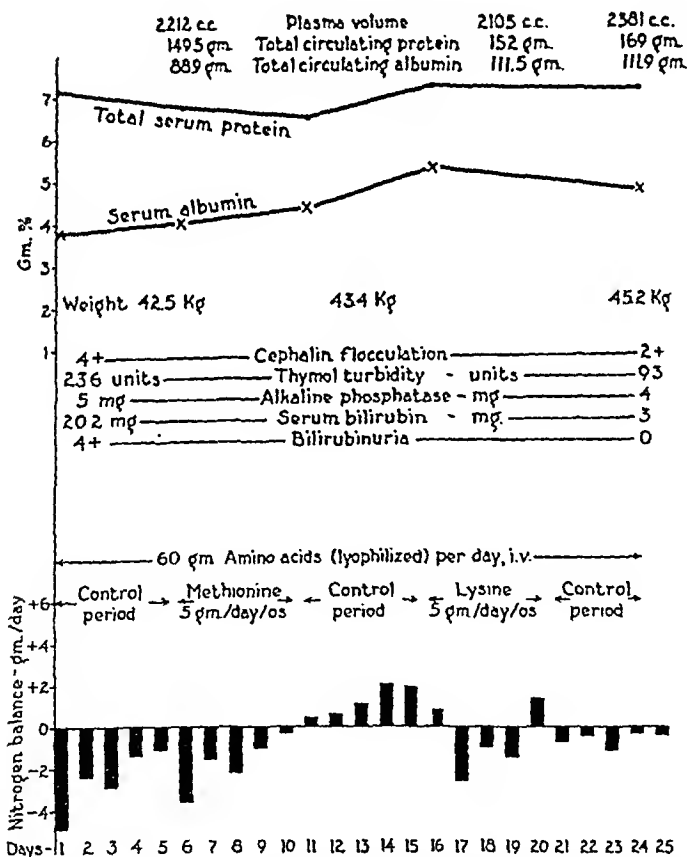


FIG. 2.—Results of studies on an 18 year old colored female who entered the hospital after 1 week of prodromal symptoms (malaise, anorexia and occasional vomiting) and 2 weeks of jaundice. The liver and spleen were both 2 fingers below the costal margin. There was a secondary anemia (R.B.C., 3.72 million; H.B., 53; W.B.C., 7000 with 66% polys). The experiments started on the 18th day after outbreak of jaundice. Because of delayed recovery the patient was discharged 4 weeks after the end of the experiment.

† Provided in 0.5 gm. tablets (Neonine) by Wyeth, Inc., Philadelphia, Pennsylvania.

‡ Provided as powder by Interchemical Corporation, Union, New Jersey.

of the experiment it markedly increased when the patient recovered.

The supplemental feeding of methionine did not significantly influence this process of gradually improving nitrogen balance. Even the 2 patients who received inadequate amounts of nitrogen and who were fed methionine, when the nitrogen balance

were daily variations in the nitrogen balance partly due to variations of the fecal nitrogen excretion. However, averages taken of the total methionine period as compared to control periods, did not prove a significant nitrogen sparing effect of methionine.

The addition of lysine in 1 feeding period

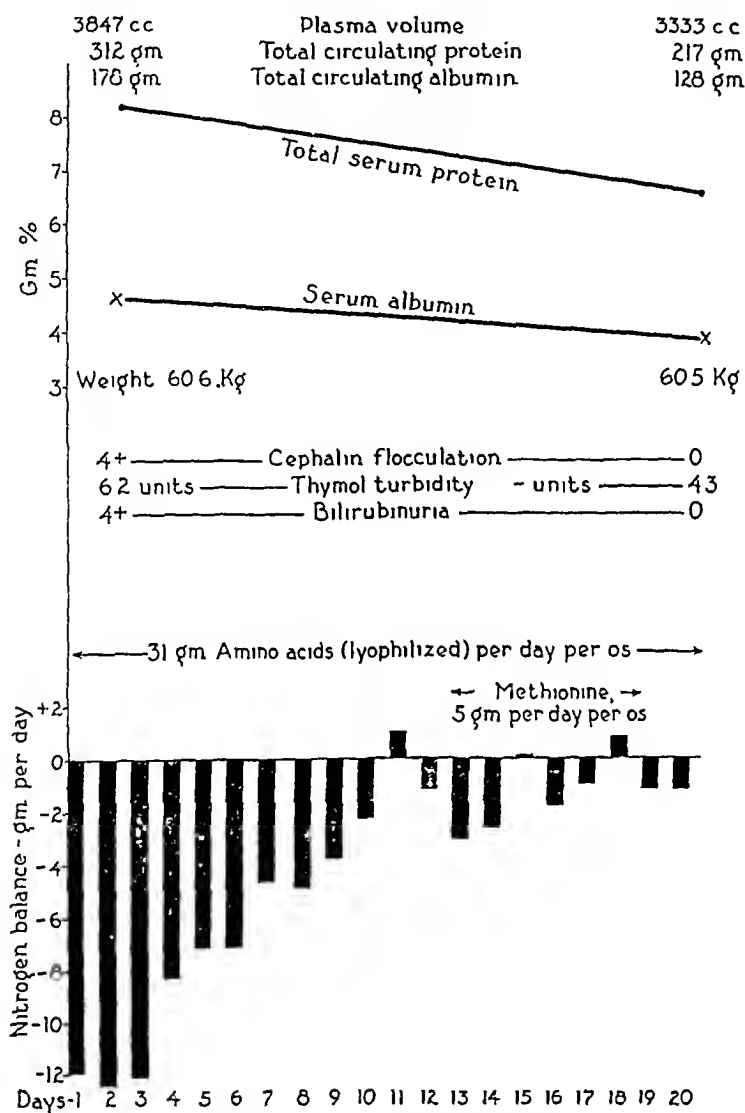


FIG. 3.—Results of studies on a 23 year old colored male who entered the hospital after 3 days of prodromal symptoms (lumbar pain, nausea, vomiting, epigastric fullness and dark urine). Liver and spleen were not palpable. The experiment started on the 7th day of jaundice and the patient was discharged recovered at the end of the experiment.

was approaching equilibrium, failed to respond. When the feeding was discontinued, the following control period revealed in all 4 patients the same general trend towards a positive nitrogen balance as during the methionine feeding. There

did not alter the general trend of the nitrogen balance nor was any change expected.

In the 2 patients receiving adequate nitrogen supply, the concentration of serum protein and albumin rose during the recovery; in the 2 other cases, with in-

adequate nitrogen supply, it dropped more or less markedly. In 2 of 4 cases (1 with adequate and 1 with inadequate nitrogen supply), the plasma volume decreased. In the one with adequate supply (Fig. 1), the rise of the serum albumin concentration resulted in an increase of

weight gain; a slight rise in the total serum protein and a more marked one in the serum albumin was mirrored in an elevation of the circulating protein and albumin. In 1 patient receiving inadequate nitrogen supply (Fig. 4), the plasma volume increased despite the weight loss.

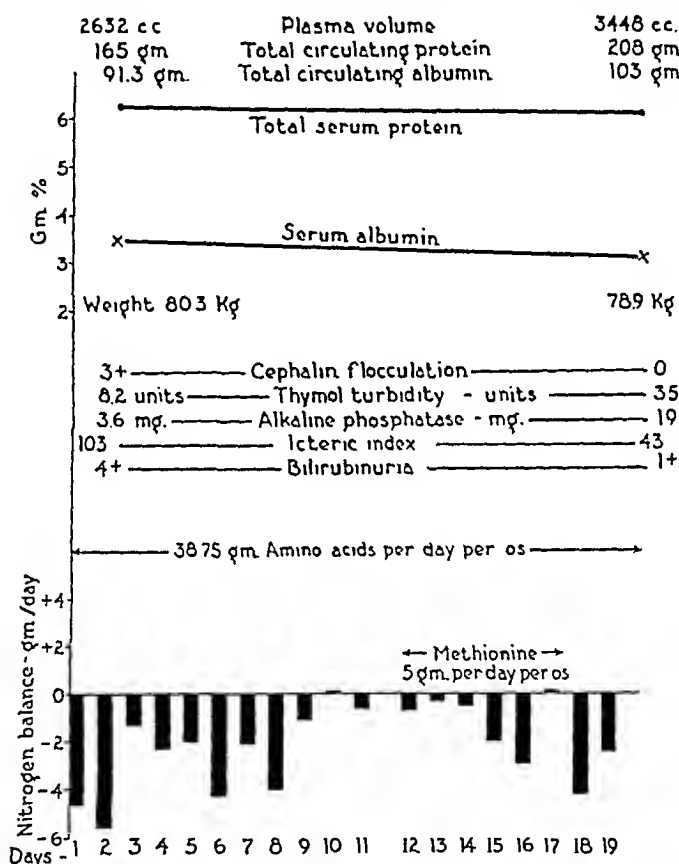


Fig. 4.—Results of studies on a 39 year old colored male who entered the hospital after 26 days of prodromal symptoms (anorexia, malaise, weight loss) and 2 weeks of jaundice. The liver was 3 fingers below the costal margin. The experiment started on the 15th day after outbreak of jaundice. The patient was slow to recover and left the hospital 4 weeks after the end of the experiment.

the total circulating serum albumin compensating for the reduction of the plasma volume. In the other patient who received an insufficient amount of protein (Fig. 3), the total protein concentration decreased, despite the reduction of the nitrogen excretion and both circulating protein and albumin markedly diminished. In the other patient receiving adequate amounts of nitrogen (Fig. 2), the plasma volume remained almost constant despite

The former caused a marked rise in total circulating protein and albumin, although their concentration dropped slightly. The total circulating hemoglobin ran, in general, parallel to the just described changes.

Comment. According to the presented experiments, methionine has no protein sparing effect in patients with infectious hepatitis. This is in contrast to the observations on dogs and other animals and in keeping with experiences on human

beings without liver diseases. A protein sparing effect is absent even in patients with markedly insufficient nitrogen supply, in which condition the sparing effect is outspoken in dogs.²⁹ It has been stated that hair formation in the furred animals is the main reason for their difference from the human in the methionine effect.

The fact that methionine, which is well utilized by patients with hepatic diseases,³⁴ has no protein sparing effect in infectious hepatitis offers circumstantial evidence against methionine deficiency in this condition, at least on the basis of current nutritional theory. Under the given experimental circumstances methionine becomes the limiting amino acid for protein formation if it should be utilized for other purposes too. If this reasoning is accepted, our studies do not provide an indication for methionine therapy in infectious hepatitis. It should be stressed that none of the examined cases were of the severe fatal type of hepatitis and also that obviously no conclusion should be drawn as to toxic hepatitis or cirrhosis.

If the methionine supplementation is disregarded, a general decrease of the nitrogen excretion is noted during the recovery stage of infectious hepatitis. This decrease indicates an increased nitrogen excretion and greater nitrogen requirements (catabolic assault³¹) during the height of the disease, as similarly found in other severe diseases. In the recovery stage, the negative balance decreases which in the face of constant nitrogen intake amounts to decreased nitrogen excretion. This decrease occurs with both adequate and markedly insufficient nitrogen supply though it is more marked in the former condition. Nevertheless, in acute hepatitis low nitrogen supply does not necessarily prevent the return of the nitrogen metabolism to normal during uneventful recovery. This does, however, not militate against the well-established fact that high protein supply may hasten recovery from hepatitis.³

In general, improvement from hepatitis is associated with a reduction of the plasma volume which increases during the height

of the disease.²⁵ During recovery also the diuresis markedly increases.^{1,23} The increase in plasma volume and the oliguria are apparently caused by insufficient hepatic detoxification of an antidiuretic principle produced by the pituitary.³²

Two of the examined cases showed this decrease in plasma volume; in a third, it did not change significantly, whereas it rose in the fourth. The changes in the plasma volume were apparently not related to the adequacy of the nitrogen intake. The total circulating plasma proteins showed in the recovery stage from acute hepatitis peculiar trends. They did not necessarily drop with decreasing plasma volume because of the increase of the plasma concentration, especially when adequate amounts of nitrogen were provided. On the other hand, with increase in plasma volume, they rose despite decreasing serum protein concentration. In general, increased plasma protein concentration is associated with increase in plasma volume. However, in recovery from acute infectious hepatitis this relation is disturbed because of reduction in plasma volume simultaneously with increase in plasma protein, the latter depending on the protein nutrition. The result of these divergent components are irregular trends of the total circulating protein. It is not clear whether these trends have physiologic significance. In contrast, the variation of the protein concentration was in apparent relation to the protein intake.

Summary. 1. Oral supplements of methionine to 4 patients with acute hepatitis (2 with adequate and 2 with inadequate nitrogen supply) failed to influence significantly their nitrogen balance.

2. The lack of a protein sparing effect in infectious hepatitis refuted the idea of a methionine deficiency which may be due to use of methionine for lipotropic or detoxifying activity.

3. During the recovery from infectious hepatitis, there is a gradual decrease of the nitrogen excretion indicating the disappearing catabolic assault which occurs

during the height of the disease. The trend for improvement of the nitrogen balance occurs also with markedly insufficient nitrogen supply. The latter did not prevent recovery from the disease.

4. In 2 cases the plasma volume decreased during the recovery from hepat-

itis. The circulating plasma proteins revealed independent variation since the rise of the protein concentration can compensate for it. The protein concentration itself, however, seemed in the examined cases to depend on the adequacy of the nitrogen supply.

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ON THE SIGNIFICANCE OF ABNORMAL FORMS OF THE BALLISTOCARDIOGRAM

A STUDY OF 234 CASES WITH 40 NECROPSIES

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As experience with the ballistocardiograph accumulated, reports have been made concerning the clinical conditions in which certain ballistic abnormalities were encountered. Thus an analysis of the first 100 cases in which the resting circulation was abnormally small was published in 1940,¹¹ and a similar study of the first 100 cases in which the circulation was abnormally large appeared in 1943.¹² The great majority of these estimates were made by calculations from the ballistocardiograms, so that these studies contained an account of the clinical conditions in which we encountered ballistocardiograms normal in form, but abnormal because their amplitude was either too large or too small.

It was planned to make a similar study of the first 100 cases whose ballistocardiograms were abnormal in form, but the war intervened before this could be accomplished. During the war it was possible to take ballistocardiograms of interesting cases from the Medical Division of the University Hospital, especially from ward patients under the charge of the senior author, so the study was continued, but war duties prevented an analysis of the material assembled. By the return of peace, ballistocardiograms abnormal in form had been encountered in 234 cases. These ballistocardiograms have been re-studied and classified according to the type of abnormality encountered, and the hospital records of the patients have been analyzed in order to discover the clinical

conditions in which such abnormalities were commonly found.

In 40 of these patients with abnormal ballistocardiograms, necropsy was later performed. Comparison between ballistocardiograms, patients' records and necropsy findings has added signally to our knowledge of the significance of abnormal records.

To summarize our findings, records abnormal in form were found chiefly in persons either with heart disease manifest by the usual clinical methods, or in conditions in which cardiac complications are known to be frequent. Improvement in form was usually accompanied by other evidence of obvious clinical improvement and *vice versa*.

When a patient with a ballistocardiogram abnormal in form came to necropsy, abnormalities of cardiac structure were present with few exceptions.

Technique. The ballistocardiograms were taken according to our usual technique,¹⁴ after a 15 minute rest period in the horizontal position, and never within 2 hours after a meal.

Abnormal forms occurring in ballistocardiograms taken in the standing position will be discussed only briefly in this paper. These records were secured after the subject had arisen from the horizontal table and stood for about 2½ minutes on the vertical ballistocardiograph.

Pulse records were taken in a few cases, using a convex tambour over the brachial artery connected with a Frank capsule. The light beam was directed into the ballisto-

cardiograph camera. Electrocardiograms, usually Lead I, were taken on the same film in many cases.

The patients were drawn chiefly from the rooms and wards of the University Hospital. A few out-patients were tested.

The Identification of Abnormalities of Form. When inspecting ballistic records one must always remember that any muscular movement may affect the record, so artefacts are frequent. A single abnormal complex, no matter how intriguing its form, is not noteworthy because the chances are overwhelming that the patient made a movement which distorted the record. Only those abnormalities which are regularly repeated are worthy of attention.

Before an abnormal complex can be identified the normal form must be known. Experience with almost 3000 records in medical students and other healthy young adults has permitted us to define it with confidence; an example is given in Figure 1-a and other examples can be found in our previous publications. Line drawings of normal and abnormal records have also been published.^{3, 15}

In normal records, near the beginning of QRS on the electrocardiogram, there is a small upward deflection, the H wave. Then at or shortly after ejection the record is sharply deflected downward, the I wave. This is immediately followed by a sharp upward deflection, the J wave, which far exceeds H in height and is the dominant peak on the normal record. This is followed in turn by the second downward deflection, the K wave, which usually approximates the I wave in depth. The lines connecting the peaks of H, I, and J are nearly straight; notches or slurs are not seen. But JK, straight in most records, may be interrupted by a conspicuous notch when the heart rate is unusually slow.

Measured from the base line, the area of the J wave far exceeds that of any other deflection in the normal record, being usually about twice the area of the preceding I wave.

The normal ballistocardiographic pattern during diastole is more variable. No waves approaching the amplitude of I, J and K are seen. A ripple is usually present and the second upward wave (N) is often higher than the first (L) as in the example given in Figure 1-a.

The waves vary in height with the phases

of the respiratory cycle, increasing during inspiration.¹⁰

These ballistic waves are a record of resultants of forces derived from the heart¹¹ and their size could be expressed numerically in dyne-seconds. We do not believe, however, that the time has come for a detailed numerical description of the record's shape. The abnormal forms of which we wish to speak can be recognized at a glance. While doubtless careful measurement would disclose deviations from the normal which we now miss, in this study we wish to direct attention to abnormalities of form so gross that they can be easily detected by inspection alone.

We have paid particular attention to abnormalities of the I and J waves, which abnormalities seem to be the commonest and most important types. Any complex is judged abnormal in form if the I wave is rounded, notched, or flattened and if its area is conspicuously reduced; or if the J wave peak is rounded, flattened, or notched, so that this peak fails to dominate the record. In many abnormal records the K wave tends to become conspicuous, not only because I and J diminish in size but also because K becomes deeper than in normal records. So while in normal records the most conspicuous wave points upward, and is the J wave, in many abnormal records the most conspicuous wave points downward, and is the K wave.

Any wave in diastole which stands out from the after-vibrations, especially if it rivals the systolic complex in height or depth, is judged abnormal.

Abnormalities of form of the H wave are so rarely encountered that we have not studied them in detail. The most common abnormality of this wave is a simple increase in its size so that it equals or exceeds the J wave in height. However, if the J wave is unduly reduced in size, the H wave is not judged abnormal if it equals the J wave. Absence of H is rarely seen but it sometimes occurs in healthy persons and so is not judged abnormal at the present time.

This discussion of abnormality of form is based on ballistocardiograms taken in

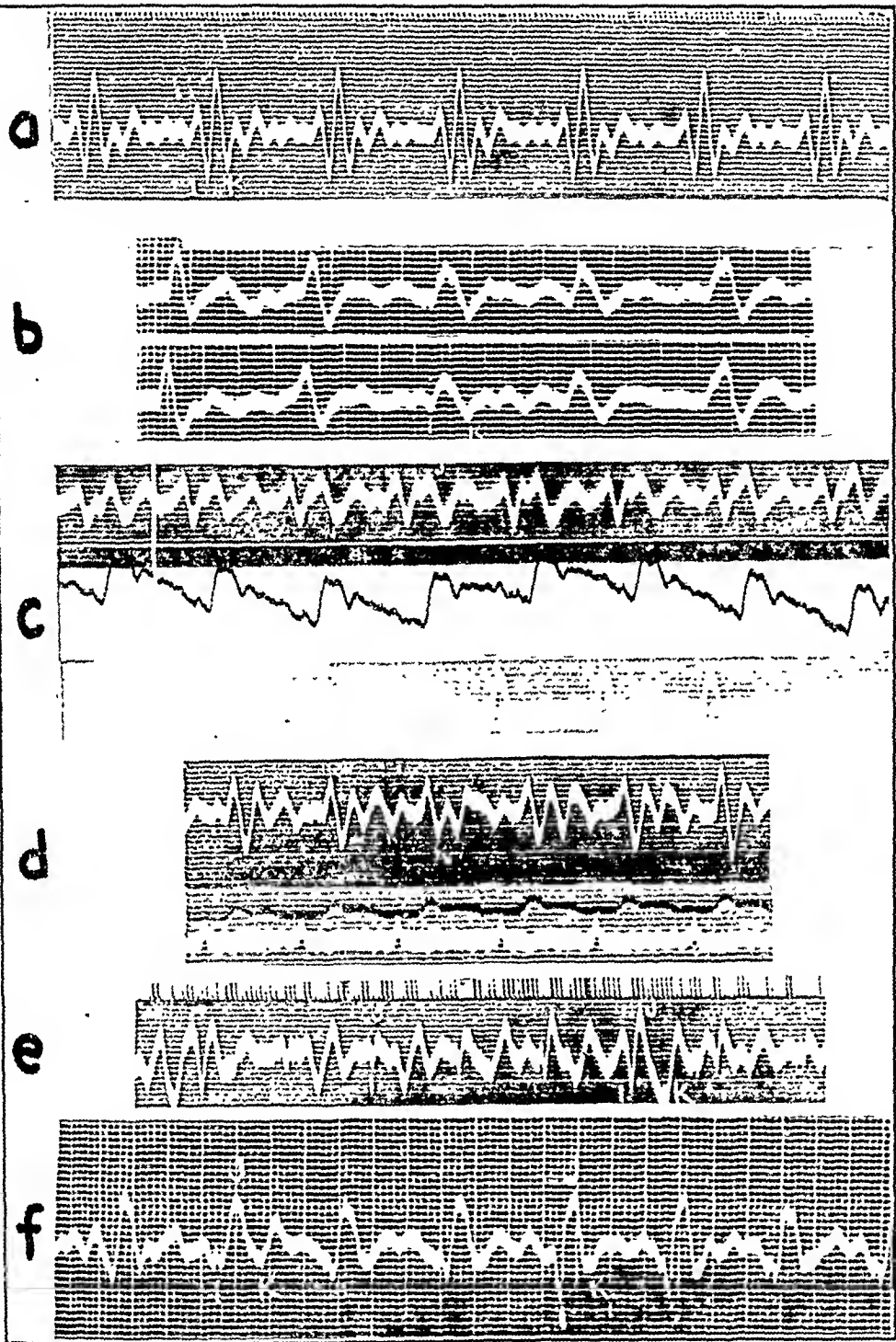


FIG. 1.—Various types of abnormal ballistocardiograms in contrast with a normal record. The time record on the top applies to all records. The reproduction is $\frac{1}{2}$ of the original size. The waves have been lettered to assist in identifying them. *a.* A normal record for comparison. *b.* C. A., age 55. Gall bladder disease, before operation. The I wave is absent in some complexes and poorly developed in the remainder. Two respiratory cycles are shown; note the similarity of the details of form in the corresponding positions in each respiratory cycle. *c.* L. B., age 45. Left bundle branch block. With electrocardiogram Lead I and brachial pulse. Note abnormal J waves. It is of interest that the pulse has a flat top also. *d.* X. R., age 47. Hypertensive heart disease in congestive failure. Venous pressure 21 cm.H₂O, B.P. 185/135. With electrocardiogram Lead I and brachial pulse. Note ballistic complexes mostly of late downstroke type. The alignment of the 3 records is perfect. *e.* M. M., age 56. Traumatic arteriovenous communication of right shoulder. Note large diastolic waves, exceeding the systolic complexes in size over part of the respiratory cycle. After surgical closure of the communication the record became normal. *f.* H. N., age 21. Normal female standing. Record shows splitting of each wave of complexes. There is a marked respiratory variation of length of splinterings.

the horizontal position, and it cannot be applied to results secured in the vertical position without reservations to be discussed later.

Results. Since the start of our work in 1937, ballistocardiograms abnormal in form have been secured in 234 cases. In compiling this and other figures several rules were necessary. When the patients came to the hospital more than once in the 10 year period, they were counted once for each admission, therefore our figures are really patient-admissions. The fact that the patients were often in a very different clinical condition at their various admissions made this method of counting superior, but patient-admissions is so clumsy a term that we will speak of the data as indicating cases. Indeed the number of repeaters was small.

A single abnormal record admits a case to our series although other ballistocardiograms taken under different clinical conditions may have been normal.

A case having more than 1 abnormal ballistocardiogram during a single admission is counted only once in our data except as follows. Often after a major surgical operation, and occasionally after a minor operation, the ballistocardiogram becomes abnormal in the immediate postoperative period, and returns to normal as convalescence is established. But a certain number of severely ill patients admitted to the surgical service for operation gave abnormal ballistocardiograms before operation, even though they had no heart disease manifest by the usual clinical studies. In all these but 1 the record became even more abnormal in the postoperative period. For this reason these cases appear in Table 2 twice, being included in the figures given for cases both before and after operation.

Ballistocardiograms abnormal in form can be classified in several ways, some of which are not mutually exclusive. The simplest and perhaps one of the most important methods, is based on the *proportion of abnormal complexes* to those that are normal. Records in which the

form varies with the respiratory cycle, the smaller complexes being abnormal while the larger ones remain normal, are very common. In such records the proportion of abnormal complexes may vary from about 20 to 100%. This method is so simple that no further explanation is required.

Much more difficult is a classification of abnormalities based on the *form of complexes*. The abnormal forms are extremely hard both to describe and classify for 2 reasons: (1) the variety of abnormal shapes encountered in different records is very great; and (2) the shape of the complexes usually varies from beat to beat in the same record. Indeed, in the most extreme examples, the record is so completely confused that it defies exact description. To bring what order was possible into our thinking, we have devised the classification recorded in Table 1. In using it readers must realize the difficulty in assigning certain records to a particular group. The different types are not sharply divided and so many intergradations occur that the senior author, reclassifying a large series of records after an interval of several months, by no means obtained exactly the same result as in the first instance.

Despite such difficulties, the abnormalities of form can be readily divided into 2 main groups. In the first, the beat to beat variation in form is so great that no classification based on form can be applied; in the second, although the form usually does change somewhat from beat to beat, a single abnormality so predominates that a classification can be based on it. These 2 groups form the basis of the classification given in Table 1.

A further subdivision of these 2 types has also been attempted in Table 1. In 69 instances the *confused records* occurred in cases in which the electrocardiogram demonstrated an abnormal rhythm or a conduction defect. So this group can be readily subdivided according to the electrocardiographic findings. In the balance of this group, in 36 instances, the irregular

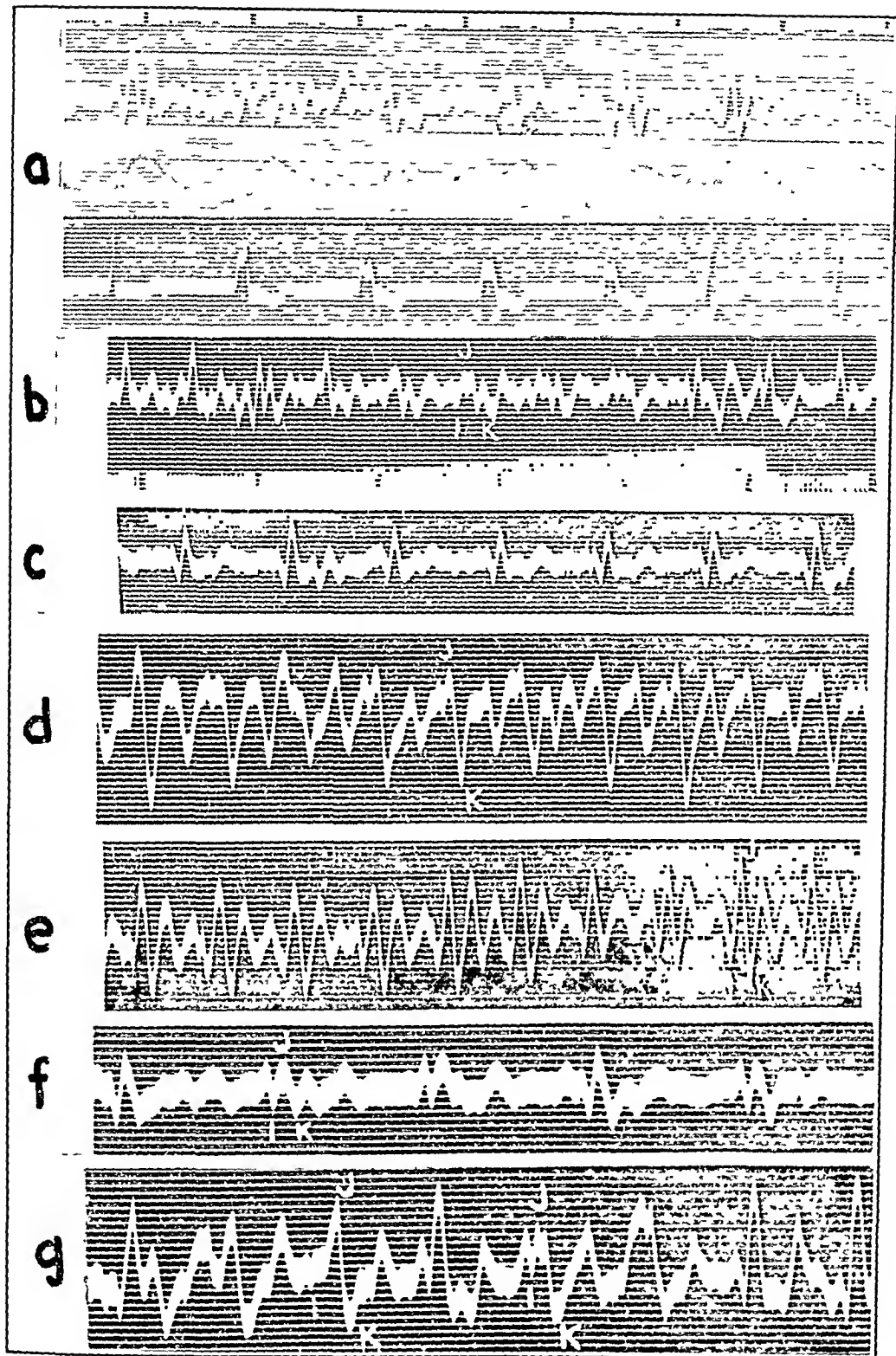


FIG. 2.—Ballistocardiograms showing various types of abnormality of form. The time record on the top applies to all records where time is not shown. The largest interval is 1 second. In the reproduction the reduction in size is not exactly uniform, the various ballistocardiograms being reduced to from 60 to 75 % of their original size. *a.* N. K., age 63. Luetic heart disease. Ballistocardiogram simultaneous with brachial pulse and Lead II of electrocardiogram. Note normal ballistocardiogram and steep ascent of pulse when electrocardiogram approaches normal, abnormal ballistocardiogram and slow ascent of pulse when electrocardiogram shows defective intraventricular conduction. *b.* L. W., age 13. Hyperthyroid heart disease. B.P. 160/90, BMR +34. Electrocardiogram negative. Orthodiagram silhouette top normal. Note very abnormal ballistocardiogram, varying with the respiratory cycle. *c.* E. W., 3 months later, on thiouracil. B.P. 126/82, BMR +5. The ballistocardiogram has returned to normal. *d.* H. K., age 53. Essential hypertension, lying at rest. B.P. 288/104. Note extremely abnormal record. Complexes of the late downstroke type predominate. *e.* H. K., 10 minutes later, after arising. B.P. 272/140. The ballistocardiogram is much more normal. *f.* E. K., age 52. Essential hypertension suspected; at rest, B.P. 145/72. Amplitude small but form is essentially normal. *g.* D. K., 15 minutes later, lying at rest immediately after mild exercise. B.P. 190/90. Only an occasional complex is normal, in the rest the abnormality varies from beat to beat with the respiratory cycle.

variations in shape could not be assigned to a cause detectable by the electrocardiogram. In these instances, at least part of the beat to beat variation accompanied the respiratory cycle.

abnormality so predominated that a classification was possible. The result is recorded in Table 1. It must be remembered, however, that included in Table 1 are many records which contain both normal

TABLE 1.—OCCURRENCE OF DIFFERENT TYPES OF ABNORMALITY OF FORM

Type of abnormality	No. cases showing abnormality listed
I. Confused records, form varying from beat to beat, no type of abnormality predominating	105
A. Cases with electrocardiographic abnormalities:	
With auricular fibrillation	42
With flutter	2
With A-V or intraventricular block	16
With multiple extrasystoles	9
B. Cases in normal sinus rhythm and without abnormalities mentioned under A	36
II. Records with a predominant abnormal form	129
A. Occurring during systole:	
Abnormality of I wave only	30
Abnormality of J wave only	32
Both I and J waves abnormal, K not deep	17
I and J low, K deep (late downstroke type)	29
Abnormalities of the H wave only	7
B. Occurring during diastole	14

TABLE 2.—FREQUENCY OF BALLISTOCARDIOGRAMS ABNORMAL IN FORM IN DIFFERENT CLINICAL CONDITIONS (EXPERIENCE FROM 1937 TO 1947)

Diagnosis	Total No. cases studied	No. cases with abnormalities of form	% with abnormalities of form
Hypertension	176	69	39
Hyperthyroid	112	13	12
Hypothyroid	22	2	10
Organic heart disease:			
Rheumatic	95	43	45
Coronary	127	63	50
Luetic	21	6	29
Congenital	34	2	6
Pericarditis	12	4	33
Type in doubt	14	3	21
Conduction defect in ECG (primary classification in doubt):			
A-V block	6	6	100
Intraventricular block	17	4	24
No manifest heart disease			
Cases from the Medical Service:			
Pulmonary disease	37	7	19
Anemia	30	2	7
Severe diabetic acidosis	3	3	100
Others		7	
Cases from the Surgical Service:			
Before operation—Colonic lesions	13	7	54
Gastric lesions	12	4	33
Cranial lesions	11	2	18
Biliary tract lesions	17	4	24
Herniæ	31	2	6
After operation — (From 1 to 10 days postoperative)	63	39	62

When there is a *dominant abnormal form* a subdivision can be based upon the wave, or waves, chiefly distorted. Thus, in 129 instances, while there was almost always some beat to beat variation in accord with the respiratory cycle, a single type of

and abnormal complexes. It is according to the form of the abnormal complexes that the classification given in Table 1 has been made.

The Clinical Conditions in Which Ballistocardiograms Abnormal in Form Were En-

countered. The cases were classified according to the usual clinical diagnoses and the results are shown in Table 2. When a patient had more than 1 of the conditions appearing in Table 2 the following rules were used. Rheumatic heart disease, coronary heart disease (angina pectoris or cardiae infarction), syphilitic heart disease, and congenital heart disease took precedence over the other diagnoses. A patient with angina pectoris and hypertension was classified under coronary heart disease only, as coronary heart disease is much more likely to render the ballistocardiogram abnormal. Cases of hyperthyroidism and hypothyroidism (Figs. 2-b and 2-c) fell easily into distinct groups according to the basal metabolic rate. Cases were classified as having auriculo-ventricular or intraventricular conduction defects only when the primary diagnosis was unknown or uncertain.

cases these abnormalities occurred when no cardiac abnormality was suspected from the routine clinical examination, or to be anticipated from the type of disease.

The Occurrence of Ballistocardiograms Abnormal in Form at Different Ages. Our data on this point were summarized in Table 3. There will be seen the number of abnormal records encountered in each decade and their relative frequency in the patients encountered in our studies.

The value of the data is limited by the fact that a general survey of the population was never attempted, and the very nature of the test leads to a greater interest in testing cases suspected of heart disease. Thus the pediatricians were inclined to refer to us only those children in whom heart disease was suspected and this affected our statistics in the younger age group. Similarly in the adult groups, while in the early years of the work all

TABLE 3.—OCCURRENCE OF BALLISTOCARDIOGRAMS ABNORMAL IN FORM IN DIFFERENT AGE GROUPS

Age (yrs.)	No. subjects tested	No. showing abnormalities of form	% showing abnormalities of form
0-9	16	1	6
10-19	110	10	9
20-29	468	9	2
30-39	275	31	11
40-49	359	51	14
50-59	269	67	25
60-69	236	53	22
70-79	44	11	25
80 and over	7	1	14

Cases were classified as hypertension when the blood pressure exceeded 170/100 on at least 1 examination.

As is shown in Table 2, abnormal records were found in 50% of patients with coronary heart disease, and in a somewhat smaller proportion of cases with most forms of organic heart disease, and with intraventricular conduction defects. We found abnormal forms only rarely in congenital heart disease but the number tested was small. In the great majority of instances abnormalities of ballistie form were found in cases of manifest heart disease or those in which, like hyperthyroidism and hypertension, heart disease is a frequent complication. But in 58

clinical types were tested, in the later years our work was concentrated where the interest lay, in cases with manifest or suspected abnormalities of the heart and circulation. Also we tested large numbers of medical students and this has affected the results in the 20 to 29 year group.

Obviously, therefore, the proportion of abnormalities found is of limited value, as it applies only to our special experience. But the data show clearly the one point we wish to make; that is, abnormalities of impact form occur far more frequently in persons over 50 years of age.

Variation of Form With Changing Clinical State. Our records are full of instances of this and many have been published.

Persons suspected of a cardiac abnormality but having a normal ballistocardiogram at rest may show an abnormality of form if they are tested after exercise; an example is given in Figure 2-f and 2-g.

In patients with manifest heart disease, the administration of digitalis is frequently followed by great improvement in the form of the record.⁷ Interestingly enough, given ill-advisedly to a man with a normal heart, the drug caused marked abnormalities of form in 1 case.⁷

After severe surgical operations the ballistocardiogram often becomes abnormal in form and it usually returns to normal during convalescence.³

In a patient with a functioning tumor of the adrenal medulla, the ballistocardiogram became abnormal in form during the attacks of extreme hypertension.⁴

In several cases of profound anemia the records were abnormal in form and they returned to normal after the blood count and hemoglobin improved.

In manifest cardiac disease clinical improvement is often accompanied by striking improvement in the form of the ballistocardiogram.^{5,7}

Without attempting a complete catalogue of such experiences it may be stated that our records abound with instances in which clinical improvement has gone hand in hand with improvement in ballistic form, and in which a setback has been accompanied by the development of abnormalities of ballistic form. The reverse has not been seen.

Ballistocardiographic Variations in Form Present in the Standing Position. As soon as the first vertical ballistocardiograph¹³ had been constructed it was noted that many of its records were more confused than those taken in the horizontal position. Some of this distortion was obviously due to vertical vibrations in the building, but for the most part it seemed due to involuntary muscular movements of the patient, movements often exaggerated to the point of obvious tremor in those patients who were severely ill or who had been long confined to bed.

After the construction of the portable models with electrical amplification,³ the records obtained in the horizontal position differed in no way from those secured by our first machine, but we are beginning to realize that the records obtained in the vertical position by our newer instrument are to some degree clearer and less distorted than those secured by our first apparatus. There may be more than one reason for this, but an obvious factor lies in the fact that the newer portable instrument has been set up in parts of the hospital far away from the jerky elevators which are so close to our original vertical machine. Doubtless for this reason the newer instrument does not require the heavy weighting and elastic cushioning that was essential to the earlier instrument.

In any event, the junior author, who had charge of a wartime investigation with the newer instrument, observed certain features of the normal vertical record which the senior author, whose experience was almost altogether with the older instrument, had overlooked. After attention was called to them these features could be easily seen in the records secured by the older instrument as well.

An analysis was made of 119 records taken on 32 normal subjects standing on the newer vertical ballistocardiograph. In practically all of these records, there was a splitting or a splintering of the I and J waves in most of the complexes, the result being a complex which had an I wave of much smaller area in proportion to the J wave than in the normal horizontal records. These deviations from the expected normal cannot be explained as artefacts from a rapid vibration entering the record from without, because they have a definite pattern varying with the phases of respiration. A good example of this is shown in Figure 1-f. At full inspiration the I wave is deep and narrow the J peak slurred with the highest point back; at expiration the I wave is broader with 2 downward peaks, the J peak flattened, often with the high point forward. In the example given in Figure 1-f these

features are more pronounced than is usual; many gradations between this and the expected normal are found.

Obviously, therefore, there may occur in apparently healthy persons when standing upright, deviations from the form established as normal for the horizontal position.

A COMPARISON BETWEEN BALLISTIC FORM AND SUBSEQUENT NECROPSY FINDINGS. Fifty-three patients on whom ballistocardiograms were abnormal in form are known to have died and necropsies were secured on 40 of them. The essential findings are recorded below; only those concerned with the heart and aorta are given in any detail; the rest of the picture is indicated under the heading "diagnosis". Blood pressure, always taken at the time of the time of the ballistocardiogram, is recorded only if it was abnormal. Microscopic findings are not given when they merely confirmed the gross pathologic diagnosis. When an electrocardiographic abnormality was known to be present, this is stated.

downstroke type. Died 2/9/43. *Necropsy*: heart (240 gm.) firm, reddish tan; aortic 5, pulmonic 7, mitral 6, tricuspid 12 cm.; marked thickening, shortening and fusion of the mitral and aortic cusps. The rigid valves are about 80% closed. Myocardium measures: L.V. 12 mm., R.V. 10 mm. R.V. is hypertrophied and dilated. Microscopic: myocardium is normal; 1 fibrosed Aschoff body in the subepicardial fat. *Diagnosis*: chronic rheumatic heart disease with mitral and aortic stenosis, passive congestion and arteriosclerosis of lungs with R.V. hypertrophy, multiple pulmonary infarcts and hydrothorax.

C. H., aged 56; ECG intraventricular conduction defect; ballisto. 10/28/37, with ECG and pulse, most confused. Ballisto. 11/5/37 with ECG, similar. Ballisto. 11/18/37 with ECG, extreme confusion. Died 12/9/37. *Necropsy*: heart weighed 890 gm. All the chambers are dilated, the left ventricle measures 3.5 cm., at the apex it is less than 1 cm. Here the myocardium becomes gray and somewhat fibrous. The coronary arteries show no evidence of an occlusion or thrombosis. Microscopic: muscle fibers of the left ventricle are prominently enlarged. In a

TABLE 4. PRIMARY CARDIAC DIAGNOSIS MADE AT NECROPSY WHEN BALLISTOCARDIOGRAM WAS ABNORMAL IN FORM DURING LIFE

Primary cardiac diagnosis	No. cases
Cardiac infarction	8
Rheumatic heart disease	7
Coronary disease without infarction	3
Hypertrophy—associated with hypertension	4
Pericarditis	2
Syphilitic heart disease	1
Congenital heart disease	1
Advanced amyloidosis of heart	1
Hypertrophy and dilatation (origin unknown)	1
Cardiac lesions of doubtful significance	3
Essentially normal*	9

* In 8 the record was abnormal only immediately after surgical operation.

We are, of course, indebted to the many members of the Pathological Department, who performed the necropsies. One necropsy has already been reported,⁷ the others follow. A brief summary is given in Table 4.

J. R., aged 37; ballistocardiograms taken 9/14/42, 1/4/43 and 1/14/43; extremely confused records with the form varying from beat to beat; only an occasional normal complex; small systolic complexes of the late

large area the musculature is completely replaced by a dense fibrous tissue; the smaller branches of the coronary vessels show little thickening of the medial coat. *Diagnosis*: myocardial dilatation and hypertrophy with left ventricular apical infarction.

H. S., aged 62; B.P. 170/80; ballisto. 10/31/40, runs of coupled beats (too much digitalis?); I waves are shallow and J flat. Ballisto. 11/14/40; record completely confused, respiratory impacts prominent. *Necropsy* (1/29/41): heart weighed 850

gm., all chambers are dilated and hypertrophied, no infarcts or fibrous areas were found; the valves were essentially normal; coronaries have patchy yellow intimal plaques, but are large and patent throughout. Microscopic: hypertrophy and focal fibrosis. *Diagnosis:* cardiac hypertrophy (marked) and dilatation (moderate); dilatation of aortic and pulmonic valve rings. Kidneys: benign nephrosclerosis with healed pyelonephritis. Comment: the amount of hypertrophy was recorded as remarkable, especially when compared to the insignificant renal changes.

J. M., aged 36; ballisto. 1/31/39; I is abnormally small even in the most normal complexes. When the breath is held in expiration I-J is slurred or notched; this is also true of the small complexes when he breathes normally. Died 5/12/40. *Necropsy:* heart (550 gm.) had old fibrous adhesions between the 2 layers of the pericardium at the base of the heart. The right and left ventricle and the right auricle are hypertrophied and show small gray areas of fibrosis. The right ventricle and auricle are dilated. There was severe fibrosis and stenosis of the mitral valve ("fish-mouth type"). The aortic valves are thickened; along the margin of the cusps are numerous minute vegetations. Microscopic: muscle fibers are hypertrophied. Many small foci of interstitial fibrosis, mostly perivascular, some containing lymphocytic and epithelioid cells. *Diagnosis:* rheumatic heart disease (active); mitral stenosis and insufficiency, verrucous vegetations on the valve margins, hypertrophy of the right ventricle (severe), dilatation of the right auricle (marked), cardiac hypertrophy.

H. K., aged 47; B.P. 98/72; ballisto 4/6/46. Form varies from beat to beat and almost no normal complexes are seen. Part of this variation from beat to beat is respiratory, but part is not as is demonstrated by a simultaneous record of respiration. In the small complexes J equals or is less than H in height, and I does not nearly reach the baseline. In some, H, I and J are almost flat; in others, a notch is produced; in these complexes K is deep. The whole record looks very confused. Died 5/21/46. *Necropsy* showed generalized amyloidosis. The heart (540 gm.) is especially involved; left ventricle was thicker than normal, right auricle contained a large adherent fibrous thrombus. Pericardium and valves were negative. Coron-

aries were normal. The cut surface of the L.V. showed several old fibrous streaks. Sections showed a diffuse infiltration of the myocardium by amyloid and much of the remaining muscle stained poorly; nuclei and striations lost. *Diagnosis:* cardiac hypertrophy; mural thrombus, right auricle; amyloidosis. This was a striking case of primary amyloidosis. The amyloid was present in every muscle examined and in every organ except the kidney and prostate.

L. O., aged 54; cancer of the lower esophagus. Ballisto. 5/19/44; normal in form. Ballisto. 5/24/44; followed a transfusion by 3½ hours; at the time of the test the patient felt weak and chilly. The record was somewhat abnormal in form, J being flattened or notched in the smaller complexes so that it scarcely exceeded H in height. The operation (5/25/44) was a rib resection and subtotal gastric resection; a splenectomy, an esophagectomy using the transthoracic approach, and a gastrostomy. Ballisto 6/7/44; highly abnormal; rate 115; form varied from beat to beat. Practically no normal complexes were seen, and the appearance was one of great confusion. Ballisto. 6/10/44; completely different from any of the preceding ones; the amplitude was very small; J was conspicuously absent or much reduced. In many complexes J was deeply notched; in others, flat. Only an occasional normal complex was seen. *Necropsy* (6/12/44): heart (350 gm.) was essentially normal. The main pulmonary artery contained a few small, soft, reddish gray, branching thrombi. The right pulmonary artery was completely occluded by a mass of twisted adherent branching thrombi, some as much as 1 cm. in diameter. The smaller branches contained secondary thrombi. The left lung showed a few smaller thrombi. *Diagnosis:* pulmonary thromboses.

H. J., aged 66; ballisto. 6/12/44; normal in all respects. An exploratory laparotomy (6/13/44) disclosed carcinomatosis of abdominal cavity. Ballisto. 6/19/44; an abnormal record, the J waves being reduced on amplitude, notched or flattened. The form varied from beat to beat. Ballisto. 6/21/44; a larger amplitude but the abnormalities in form remained the same and very few normal complexes were seen. *Necropsy* (6/27/44): heart was essentially normal. The tumor mass was primarily in the colon with metastases to many other organs.

R. S., aged 34; carcinoma of the pharynx; ballisto. 4/4/44, before gastrectomy; normal in form but abnormally small. After gastrectomy permitted better feeding, the patient's general condition improved and the ballistocardiograms became larger. Those of 4/20, 4/24 and 4/25 were all normal in form. The record of 4/26 is not altogether normal as there is a slight notching of J in the smaller complexes. On 5/11/44 the records were normal again. *Necropsy* (6/25/44): extreme emaciation; heart weighed 150 gm. (about one-half the normal size for this age). It was of the usual shape and firm in consistency. Pericardium, valves, ventricular muscle, coronary arteries and sections all showed nothing abnormal. Cause of death: hemorrhage from carotid artery. The primary site of the neoplasm was never determined.

J. B., aged 46; ballisto. 7/2/45 and 7/5/45; both normal. He had a craniotomy on 4/6/45 and on 7/12/45 the ballistocardiogram was extremely confused; only the largest complexes were normal and the balance of form varied from beat to beat, small I waves and deep K's being prominent. On 7/21/46 the ballisto. had returned to normal. *Necropsy* (9/22/46): heart was entirely normal. Cause of death: meningioma of the olfactory groove.

G. L., aged 42. Before any ballistocardiograms were taken the patient had had a cerebral arteriogram, on 6/5/45. The first ballisto. on 6/7/45 was normal. On 6/28/45 the record was not altogether normal as some small complexes lacked the I wave. On 6/29/45 craniotomy was performed. On 7/5/45 the ballistocardiogram was grossly abnormal. No normal complexes were seen, the I wave being diminished or absent in all complexes. On 7/10/45 the ballisto was normal once more. *Necropsy* (7/31/45): the heart was normal. *Diagnosis*: astrocytoma of the left frontal lobe.

L. B., aged 68; ballisto. 5/16/45; only the largest complexes are normal, all the others lacking I waves almost completely. In many complexes the notch of I does not reach the baseline. On 5/17/45 an ileocolostomy was performed. Ballisto. 5/22/45; no normal complexes seen, the impact form varied from beat to beat. The I wave was never well developed and many complexes were of the typical late downstroke type. Ballisto. 5/29/45 had improved; there was considerable tachycardia; rate 115; most complexes

were normal but an occasional one showed a notched J wave. *Necropsy* (6/19/45): heart (300 gm.) was extremely soft and flabby; the valves and coronary arteries were negative. There was a minimal fibrous pericarditis; the sections showed nothing abnormal. *Diagnosis*: tuberculosis of the cecum; tuberculous peritonitis.

J. T., aged 15; ballisto. 9/26/45; normal. On 9/27/45 he had an abdominal perineal resection. A ballisto. was taken on his way back from the operating room; in it the I wave was diminished or absent in all complexes. Ballisto. 10/3, 10/9 and 10/16/45; normal. *Necropsy* (1/7/46): the heart was normal. *Diagnosis*: primary carcinoma of the rectum with multiple peritoneal metastases.

W. W., aged 43; ballisto. 7/9 and 7/12/45; normal. On 7/19/45 he had a craniotomy for brain tumor right fronto-parietal region. On 7/19/45 the ballisto. was so confused by tremor that it could not be read. He was having convulsions at the time. Ballisto. 7/24/45 showed increased respiratory arches but the cardiac complexes were normal. Later in the day he had a sudden attack of dyspnea and became cyanotic. He died next day. *Necropsy*: heart contained a mural thrombus in the right auricle but was otherwise negative. The main pulmonary artery was occluded by a firm red thrombus. *Diagnosis*: a subcortical tuberculoma.

H. L., aged 56; ballisto. 9/15/42; rate 112; large amplitude; I not well developed. Ballisto. 9/18/42; rate 90; complexes more distorted. H-I hardly more than a notch or slur; some complexes of late downstroke type. Ballisto. 10/12/42; rate 98; large complexes now normal; small ones of late downstroke type. Record improved since last test. *Necropsy* (7/18/44): heart (550 gm.) is markedly enlarged, especially L.V. A bulging infarct of the anterior wall of the L.V. near the apex is extremely soft and hemorrhagic; the myocardium is thin and markedly softened. The coronary arteries (examined by radio-opaque injection) show sclerotic plaques; marked narrowing near the orifice of the anterior descending and a thrombus occluding the right coronary 6 cm. below its orifice. *Diagnosis*: hypertrophy and dilatation of the L.V., old anterior myocardial infarction with mural thrombus. Severe coronary arteriosclerosis with occlusion of right coronary.

E. M., aged 50; ballisto. 10/25/38; auricular fibrillation; systolic complexes very abnormal, form varying from beat to beat. Late M and late downstroke complexes are seen, and there is occasionally a large complex in diastole. *Necropsy* (6/8/41): heart (610 gm.) is reddish brown and rather flabby; all chambers are dilated and hypertrophied. Mitral valve is greatly thickened and rigid with some calcification; chordæ tendinæ thickened and shortened. The aortic valve has slight nodular thickenings. The coronaries are patent. Microscopic: in the L.V. large patches of muscle fibers have been replaced by dense scar tissue with embedded dilated thin-walled vessels. *Diagnosis*: chronic fibrous endocarditis, mitral valve, with stenosis and insufficiency, marked diffuse myocardial fibrosis; hypertrophy and dilatation; mural thrombi. *Remarks*: this is a straightforward case of rheumatic heart disease. Cerebral emboli were the cause of death.

M. F., aged 30; ballisto. 10/14/37; the amplitude is very small; in one place flat J's are seen but the rest of the record seems normal in form. *Partial necropsy* (1/19/38): heart (300 gm.): R.V. is moderately dilated (wall 0.6 cm. thickness). Mitral valve measures 9 cm.; its cusps are thickened; to them are attached friable, red vegetations. Similar vegetations are found on aortic valve. *Diagnosis*: old rheumatic endocarditis with typical subacute bacterial endocarditis.

A. H., aged 38; ballisto. 12/14/37; auricular fibrillation; form varies markedly from beat to beat and is usually highly abnormal. *Necropsy* (2/26/38): heart (455 gm.) firm, reddish brown. Pericardial cavity contained 100 cc. of blood-tinged fluid. Mitral orifice much stenosed; cusps are irregularly roughened and calcified. Myocardium measures: R.V. 0.9 cm., L.V. 2.8 cm. *Diagnosis*: mitral stenosis, dilatation and hypertrophy of right heart; thrombi left auricular appendage.

S. M., aged 45; ballisto. 12/21/39; I seems unusually large in proportion to J which it equals in area in most complexes; nothing else abnormal was seen. ECG minor grade A.V. block, ventricular extrasystoles, severe myocardial damage. *Necropsy* (4/20/39): heart (830 gm.) firm; myocardium measures: L.V. 3 cm., R.V. 0.8 to 1.2 cm. Aortic valve shows marked thickening of cusps with much stenosis. The coronaries are widely patent. Microscopic: chronic myo-

carditis and chronic pericarditis. *Diagnosis*: hypertrophy of both ventricles. *Remarks*: the diagnosis of rheumatic heart disease was favored though the findings were not characteristic.

A. J., aged 56; ballisto. 9/11/42; respiratory impacts prominent, cardiac impacts very small; systole cannot be identified with certainty. Ballisto. 10/23/42; respiratory impacts still prominent and systole is still impossible to identify with certainty. Complexes very small, and beat to beat variation apparently great. Ballisto. 12/14/42; the Cheyne-Stokes respiration; huge respiratory impacts during breathing period overwhelm the record; during apnea systolic complexes are plainly seen and they are of a most unusual shape. The rate is slow, 48. Without a simultaneous ECG I am a little uncertain of the interpretation but I suspect that a stopping complex dominates the record and that the starting complex is of the late downstroke type. ECG left bundle branch block. *Necropsy* (2/27/43). Heart weighed 620 gm. Three main coronary arteries all extremely sclerotic with small lumina anterior descending and is completely obstructed. Marked myocardial atrophy, numerous recent and old organized interstitial hemorrhages, degeneration, recent coagulation necrosis and fibrosis. *Diagnosis*: coronary sclerosis, recanalizing occlusion of left artery, myocardial infarction and fibrosis. *Remarks*: this is a classical example of coronary occlusion and progressive heart failure.

F. T., aged 34; ballisto. 5/10/44; record is so confused that the cardiac rhythm cannot be made out, nor can the systolic impacts be identified with certainty. Form varies from beat to beat in an irregular manner. ECG 5/1/44 showed auricular fibrillation, rate was 79. All complexes were unusually small. *Necropsy* (5/11/44): heart (820 gm.) soft and flabby; extreme enlargement and dilatation of all chambers; the valve leaflets are normal; coronary arteries patent. Multiple sections showed no evidence of disease in the myocardium. *Diagnosis*: hypertrophy and dilatation (all chambers of the heart); mural thrombus, right auricle. Cause of death was multiple infarction of the lungs. Primary diagnosis: hepatitis.

M. R., aged 59; B.P. 150/40; ballisto. 12/12/39; there is a high diastolic wave

equalling or exceeding J wave during inspiration but lower during expiration. The systolic complexes are normal. ECG showed minor grade heart block in Leads I and II. *Necropsy* (3/25/40): heart (820 gm.) is enormously enlarged, especially to the left. There are fibrous epicardial adhesions. The wall of the L.V. is thickened and its chamber very much dilated. The septum bulges into the R.V., materially reducing its capacity. All of the valve rings are dilated, especially the aortic and mitral rings. The aortic cusps are large; the valve margins fibrous and thickened. The coronary orifices are slightly narrowed and sclerotic, but otherwise the arteries are not remarkable. Microscopic: muscle fibers are hypertrophied and there is marked interstitial edema. There is no myocardial necrosis or fibrosis. *Diagnosis*: syphilitic heart disease, syphilitic aortitis with diffuse aneurysmal dilatation of the aorta, severe; aortic insufficiency; cardiac hypertrophy and dilatation; fibrous epicarditis.

B. S., aged 56; B.P. 180/120; ballisto. 12/4/37; form varies from beat to beat and is so confused that a dominant rhythm is hard to identify with certainty. There is very marked respiratory variation. *Necropsy* (3/24/38): heart (850 gm.) is dilated. Myocardium of R.V. is light reddish brown and flabby. There is an infarcted area in the left anterior wall several cm. across, extending onto the ventricular septum; valves are essentially normal. The left anterior descending coronary artery is occluded 2 cm. from the orifice. Below this the vessel is calcified and the lumen barely admits a pin. The right coronary is narrowed but no definite block. Microscopic: much replacement of muscle fibers by dense fibrous and hyalinized tissue. *Diagnosis*: coronary sclerosis and thrombosis with massive infarction of left ventricle, both recent and old.

H. T., aged 13; ballisto. 10/20/37; small complexes of late downstroke type. A few of the larger complexes are normal. Ballisto. 11/3/37; smallest complexes now extremely abnormal; H, I and J almost absent; K remains prominent; a few large complexes remain normal. *Necropsy* (12/22/37): several hundred cc. of serosanguinous fluid in the pericardial cavity: a shaggy gray fibrinous mass completely envelopes the heart. Microscopic: pericardium is greatly thick-

ened and contains large foci of caseation and necrosis. A few small distinct tubercles. *Diagnosis*: tuberculous pericarditis; miliary tuberculosis of the lungs.

H. P., aged 63; ballisto. 1/11/45; while the large complexes are normal, the small ones are grossly abnormal; their form varies, in some J is almost flat; in others J is distorted and K deep. *Necropsy* (2/5/45): heart (not weighed) was covered with a hemorrhagic, fibrinous exudate; the heart muscle is soft and flabby and the chambers moderately dilated. There was no evidence of infarction or fibrosis. Coronary arteries were somewhat sclerotic. *Diagnosis*: acute fibrinous pericarditis, with hemopericardium. Primary carcinoma of lungs with metastasis to lung and lymph nodes.

D. J., aged 13; ballisto. 10/23/42; most complexes are normal. In an occasional small complex the I wave is diminished or absent but the abnormality is certainly minimal. *Necropsy* (11/10/42): heart weighed 280 gm.; coronaries are normal; pulmonary valve has shrunk cusps with rolled edges forming a single cork-like ring on the opened orifice. The other valves were normal. The foramen ovale is a 2 cm. ring bridged by a network of interlacing bands and cords but with numerous large gaps. Microscopic: myocardium normal. *Diagnosis*: pulmonary stenosis; patent foramen ovale; R.V. hypertrophy. Kidneys: sub-acute glomerulonephritis; hydropericardium; hydrothorax and ascites. Died in anasarca.

H. H., aged 56; ballisto. 9/18/42; very marked respiratory arching confuses everything and systolic complexes cannot be certainly identified. Ballisto. 9/19/42; after tapping chest, respiratory impacts are gone; tracing is of extremely low amplitude, the smallest complexes being truly tiny but their form seems to be normal. *Necropsy* (10/5/42): heart (340 gm.) contained a long coiled thrombus loose in the R.V., apparently a recent embolus. Heart was otherwise normal. *Diagnosis*: carcinoma of the right lung and pulmonary embolism; thrombophlebitis of legs.

B. H., aged 49; ballisto. 1/20/38; small in amplitude but normal in form. Ballisto. 3/18/38; many ventricular extrasystoles with coupled beats. NSR complexes normal in form but VES small and variable; all complexes of very low amplitude. *Necropsy* (3/30/38) limited to the heart only; it weighed

340 gm.; there was an old infarct 3 by 2 cm. in the anterior portion of the left ventricle and another 3 cm. in circumference in the interventricular septum. Microscopic: both infarcts were encroached on by fibrous tissue. *Diagnosis:* multiple cardiac infarcts. Former myxedema.

M. M., aged 63; B.P. 185/85; ballisto. 10/11/37; there is marked respiratory variation; the largest complexes are normal, the smallest highly abnormal. Most of these latter show a striking double J peak; all have a prominent notch on I-J. *Necropsy* (11/9/37): heart weighed 390 gm.; coronary arteries showed numerous yellow intimal thickening and small patches of calcification. Microscopic: there was hypertrophy of muscle fibers, and many separated by slender acellular fibrous strands. *Diagnosis:* hypertrophy. Patient succumbed to a combination of infection from her purulent bronchitis and the long-continued effects of a thyroid adenoma which had caused clinical symptoms for over 30 years.

J. R., aged 56; B.P. 188/110; ballisto. 3/31/39; early M type, the J peak equals or slightly exceeds H. There is a very clear complex in diastole. Died 5/6/39. *Necropsy:* heart (550 gm.) a firm reddish brown. Myocardium measures: L.V. 2 cm., R.V. 1 cm. The valves, base of aorta and coronaries show patchy sclerosis. Microscopic: heart muscle cells large, with nuclei swollen and enlarged; a fine diffuse increase of intercellular fibrous tissue. *Diagnosis:* hypertrophy of L.V., arteriosclerosis of the coronaries, adenocarcinomatosis.

E. B., aged 34; B.P. 195/135; ballisto. 10/6/38; amplitude small; large complexes are normal, small are abnormal; I is small or absent, J is often notched. Ballisto. 12/11/38; the record is confused, large forms normal, and small forms abnormal, showing a flat J. Ballisto. 1/23/39; confused. Large complexes almost normal though I is rounded, in small complexes J often notched. Area of I equals J. Large L wave gives an M appearance to small complexes. Died 1/28/39. *Necropsy:* heart (690 gm.) reddish gray. Myocardium measures: L.V. 3 cm., R.V. only 0.5 cm. Endocardium, valves and coronaries are negative. Microscopic: muscle cells are swollen and thickened, appearing pale and cloudy; their nuclei are large and boggy and some are irregularly shaped (elk horn type). *Diagnosis:* hypertrophy of the left ventricle, moderate pericardial effusion.

Histologic diagnosis: hypertrophy of the L.V., cloudy swelling. Kidneys: malignant nephrosclerosis.

P. N., aged 56; ballisto. 10/3/38: a confused record; only an occasional complex is normal. Despite the simultaneous ECG the identity of the waves is uncertain. I is poorly developed, JK is sharp, followed by an L wave often higher than J. Died 11/19/38. *Necropsy:* heart (230 gm.) dark red and soft. Myocardium measures: L.V. 1.5 cm., R.V. 0.4 cm. Coronary arteries show a few raised plaques, their lumina are widely patent. Microscopic: indistinct striations and small clumps of pigment in the muscle bundles. Liver weighed only 820 gm., about $\frac{1}{2}$ normal. *Diagnosis:* heart grossly normal. Microscopic: brown atrophy of myocardium. Necropsy did not explain cause of death.

J. G., aged 54; B.P. 210/135; ballisto. 2/3/39; only a few of the largest complexes are normal. Many large complexes show varying abnormalities of the I wave. Small complexes lack a dominant J which is often quite flat, and occasionally hardly rises above the base line. Died 5/6/39. *Necropsy:* heart (620 gm.) deep red-blue. Myocardium firm, measures: L.V. 2.3 cm., R.V. 1 cm. Endocardium, valves and coronaries are normal. Microscopic: patchy fibrosis throughout. *Diagnosis:* hypertrophy, patchy fibrosis of left myocardium. Large cyst of pancreas. It was hard to reconcile a hypertension with the almost negative kidneys. Bronchopneumonia probable cause of death.

S. E., aged 48; B.P. 170/105; ballisto. 9/24/37; cannot be found for review; it is described as showing marked pre-ejection, downward deflection. Apparently it was otherwise normal. Died 11/5/37. *Necropsy:* heart weighed 720 gm. Myocardium measures: L.V. 2.6 cm., R.V. 1.3 cm., coronaries patent. *Diagnosis:* myocardial hypertrophy and dilatation of right auricle and ventricle. Terminal infarctions of lungs.

H. K., aged 47; ballisto. 4/12/38; heart rate is regular but the record is in the greatest confusion. When breath is held the record clears up, but J is hardly larger than the other waves. ECG showed bundle branch block. Died 4/25/38. *Necropsy:* heart weighed 780 gm., pericardium normal. L.V. measures 3 cm. Coronaries are atheromatous. Microscopic: hypertrophy, fibrosis; muscle fibers in some areas appear swollen. The smaller coronary vessels show

no changes. *Diagnosis*: myocardial hypertrophy and fibrosis; coronary atheroma. Death from thrombosis of the pulmonary artery, infarction of lungs and peribronchial lymphangitis.

M. B., aged 64; B.P. 160/110; ballisto. 2/1/38; auricular fibrillation; form varies from beat to beat and very few complexes are normal. 2/7/38, N.S.R. The complexes are small and mostly abnormal, especially in the I wave. Died 10/26/45. *Necropsy*: heart (620 gm.) moderately enlarged, particularly L.V. All chambers are dilated. Coronary arteries are sclerotic and tortuous with narrowed lumina. *Diagnosis*: arterio-sclerotic heart disease. The patient died of a cerebral hemorrhage.

A. F., aged 46; ballisto. 1/6/39; a very abnormal record. No dominant J peak, late downstroke type. Died 8/29/40. *Necropsy*: heart (630 gm.) hypertrophied (both ventricles). Infarct on posterior wall of L.V. Coronary vessels small, straight, sclerotic but not occluded. The aortic valve is thickened and the edges rolled; the mitral valve slightly thickened. *Diagnosis*: hypertrophy and dilatation, coronary sclerosis with narrowing and myocardial infarction. Sclerosis of aortic valve.

C. S., aged 43; ballisto. 2/3/41; record completely confused by dyspnea. When breath is held impacts are of good amplitude and normal in form. 2/10/41, after loss of 7 liters of fluid ballisto. same as 2/3/41. 2/18/41, amplitude still large. J is notched. 2/28/41, she has lost 16 liters of fluid; form very abnormal; deep K very prominent. 3/3/41, form extremely bizarre and confused. 3/20/41, she has lost 71 pounds of fluid; K very deep, probably a delayed stopping impact. 12/10/42, complete confusion. 9/18/43 ECG auricular fibrillation. *Necropsy* (10/20/44): heart (1000 gm.) is massively enlarged, both ventricles. Tricuspid and mitral valves are thickened and contracted, and chordæ tendineæ thickened, fused and shortened. Myocardium measures: R.V. 10 to 15 mm., L.V. 20 to 25 mm.; soft and flabby. Coronary arteries are patent. Microscopic: fibers are thickened and there are scattered areas of degeneration and fibrosis. *Diagnosis*: massive hypertrophy and dilatation of both ventricles; auricular dilatation; healed rheumatic endocarditis. Liver showed early cirrhosis and fatty degeneration.

B. M., aged 19; ballisto. 3/29/43; I wave was almost always abnormal. Usually it is

little developed; an abnormal downstroke sometimes precedes I and exceeds it in size. *Necropsy* (11/21/43): heart (350 gm.) shows extreme hypertrophy and dilatation of the right ventricle and the left auricle. The aortic, mitral and tricuspid valves are sclerosed with extreme mitral stenosis (Grade IV). Myocardium measures: L.V. 1 cm., R.V. 0.6 cm. Microscopic: the mitral valve shows definite evidence of rheumatic involvement. No typical Aschoff bodies were noted. *Diagnosis*: rheumatic heart disease, hypertrophy and dilatation (right ventricle and left auricle), aortic, mitral and tricuspid valvulitis, myocarditis, mural thrombus. Patient died suddenly, probably due to cerebral involvement by a fragment of the thrombus.

H. G., aged 55; ballisto. 12/28/38, after coronary occlusion, auricular fibrillation; rate 160; extreme confusion, great beat to beat variation. Ballisto. 2/24/39, N.S.R. Very high H, deep I, J about the same as H. A very interesting early M tracing. *Necropsy* (6/7/39): heart (350 gm.) red brown; anterior tip of the L.V. is infarcted and adherent to the pericardium; here the color is grayish and the wall thin. L.V. measures 1.6 cm. Valves are negative. Anterior descending coronary occluded 3 cm. from its origin by an organizing thrombus. *Diagnosis*: coronary thrombosis with myocardial infarction; pericardial adhesion and arteriosclerosis of coronaries. Healing myocardial infarct and organizing coronary thrombus. Patient died of bacteremia and multiple liver abscesses.

These results show clearly that ballistocardiograms abnormal in form are found chiefly in patients whose hearts contain some type of structural abnormality. If one omits the patients whose records became abnormal only after operation, a group in which the records usually returned to normal before death, the evidence for this is even more striking; 28 of 32 cases (85% of those with abnormal ballistocardiograms who came to necropsy) had some important structural abnormality of the heart, as is summarized in Table 4. Of the remaining 4, 1 had a brown atrophy of the myocardium, 1 had a patchy fibrosis of the myocardium and in 2 there were advanced pathologic changes in the lungs which may well have

handicapped cardiac function by obstructing the pulmonary circulation.

Not included in the 40 cases mentioned above are 2 cases reported before.⁸ Both of these had ballistocardiograms normal in form during life, and at necropsy their hearts were normal also.

Discussion. Experience in the clinic and at the autopsy table can be summarized as follows: Never encountered in healthy young adults in the horizontal position, ballistocardiograms abnormal in form are obtained chiefly from patients who present indisputable evidence of heart disease. In the absence of such evidence, abnormalities of ballistic form are found largely in conditions in which cardiac complications recognizable by the usual clinical methods, are prone to develop. Another characteristic of these abnormalities is the tendency to occur with greatest frequency in patients after 50 years of age; that is, in the age in which the degenerative heart diseases are found with increasing frequency. Thus we have good reasons to believe that a ballistocardiogram abnormal in form indicates myocardial abnormality.

It is also true that ballistocardiograms abnormal in form were found in 58 cases in which no cardiac disease was suspected, and that in 9 cases *abnormal* ballistocardiograms were found during life although the heart was *normal* at necropsy. We believe this finding is to be expected. Cardiac drugs such as digitalis profoundly affect cardiac function, and may render the ballistocardiogram abnormal in form, but they leave no traces which can be detected by gross or microscopic examination of the heart. So it does not surprise us that disease can produce similar "functional" abnormalities, not to be detected by the usual examination or to be found at autopsy, a fact which does not diminish their importance. Many abnormalities detected by the electrocardiogram are of this type. So these results are not inconsistent with our belief that a ballistocardiogram abnormal in form

indicates a myocardial abnormality worthy of attention by clinicians.

It should also be pointed out that many cases with rheumatic and other types of organic heart disease, give normal ballistocardiograms. We have confirmed this several times at necropsy, so we have no doubt that *normal* ballistocardiograms are found frequently in patients with structurally *abnormal* hearts. Obviously, therefore, abnormality of ballistic form is not to be thought of as caused by, or as diagnostic of, the structural abnormalities recognized by the pathologist. It represents a type of abnormality of cardiac function which could not be detected hitherto, a physiologic type, usually associated with the recognized structural types of abnormality, but by no means necessarily so.

Furthermore, our experience suggests that this abnormality is serious. While we have not attempted a follow-up of our 234 cases, 53 are known to have died. Of the 4 subjects tested as normal but found to have records abnormal in form, only 1 survived the 8 to 10 year period without developing serious heart disease.⁸

We are only at the beginning of our attempts to discern the relative seriousness of the many types of abnormalities found in our records but a few impressions should be recorded here. When only the smallest complex in each respiratory cycle is abnormal in form, the prognosis is often not serious. We have followed 2 such cases for 10 years, the ballistic abnormality has remained unchanged during all this time. Now aged 62 and 63, their cardiac health has remained good, 1 recently withstood a herniorrhaphy without trouble, and both lead normal though not very active lives as college professors. On the other hand, persons giving records with every complex distorted almost always show every evidence of being seriously ill. So we believe that the percentage of abnormal complexes is an indication of the severity of the cardiac abnormality.

Experience to date does not permit us to decide which of the great variety of abnormal shapes is of most serious import, but it seems likely that the greater the distortion of the ballistocardiogram, the more serious the abnormality.

A study of this type does but little to advance our knowledge of the fundamental cause of the abnormalities of impact form. The belief that the form of the ballistocardiogram is determined by the shape of the cardiac ejection velocity curve is supported by direct experiments to be published elsewhere.² Data encountered during the present study give indirect support to this view. In Figure 2-a are shown records of a case with varying bundle branch block. When the electrocardiogram is normal the ballistocardiogram is normal also and the pulse wave rises abruptly. When the electrocardiogram is abnormal, the ballistocardiogram becomes abnormal also and the pulse rises much more slowly, evidence that the curve of ejection velocity has altered.

While many types of ballistic abnormalities of form may be thus explained, one must recall that in disease the 2 sides of the heart may not be affected similarly. Characteristic changes of form may be expected if the ejection of 1 side remains normal while the other accelerates the blood more slowly. Our best example of this, a record secured in a case of left ventricular aneurysm, has been reproduced in another publication.¹⁰ Its abnormality, an abnormal J wave, flattened or notched, the form varying with the phases of respiration, may well be characteristic of this condition. The notched J peak seen in some cases of bundle branch block may well have a similar explanation; an example is given in Figure 1-c and here the delayed rise of the pulse wave as well as its distorted peak, suggest that ejection from the left side was abnormal. But it must be emphasized that many cases of bundle branch block have normal ballistocardiograms.

If one accepts the idea that abnormali-

ties of ballistic form are due to abnormalities in the manner in which the heart ejects blood, most of our findings can be readily explained. Most cases in which the form of the ballistocardiogram varies irregularly from beat to beat have major electrocardiographic abnormalities. In auricular fibrillation and flutter, because of abnormal excitation, the heart's contractions vary in strength as well as in time, and the systolic complexes of the ballistocardiograms are accordingly distorted. In addition, irregularity of rate makes a variation in cardiac filling which tends to permit stronger beats after the longer pauses. In complete block, when the auricular beat has its normal time relation to ventricular systole, the ballistocardiogram may become normal or most nearly so, in contrast to the small and distorted complexes often seen when the 2 beats are dissociated. Obviously better filling in the first instance permits a more normal ventricular contraction.

The cases in which the form varies with the respiratory cycle can be explained similarly. A variation in cardiac filling is induced by the pressure changes of the respiratory cycle.¹⁰ Apparently the weakened heart contracts in a manner most nearly normal when it is well filled, for the ballistocardiogram is normal or most nearly approaches the normal, at the height of inspiration in all such cases; when filling is less adequate abnormalities of ejection manifest themselves and are reflected in abnormal ballistic form. This might indeed be expected from Starling's Law of the Heart.

Not so readily explained are a few irregular and distorted records not accompanied by electrocardiographic abnormalities and not varying with respiration. These records are so seldom found in any except very sick patients that experience has led us to suspect that the patient's condition is serious whenever a record of this type is seen. In some cases diaphragmatic impacts complicate the record, but these can be readily identified by their absence when

the breath is held. To explain this abnormality, we recall experience with subjects who fainted while standing on the vertical ballistocardiograph.⁶ Before they collapsed, the record was always distorted by impacts from muscular movements which may well have been purposeful, that is, designed to support a failing circulation. Perhaps some extremely ill patients utilize the same mechanism to support a failing circulation in the horizontal position. So it may well be that movements of the skeletal muscles, too small to be perceived by the unaided eye, are the cause of the completely irregular ballistocardiograms obtained in some seriously ill persons.

This study provides some interesting data on the genesis of abnormal diastolic waves. The record (Figure 1-e) of a case with a large arteriovenous communication shows such a large diastolic wave that it exceeded the systolic complex in size, over part of the respiratory cycle. After closure of the communication, the diastolic abnormality disappeared completely. It seems evident that the increased pressure in the venous side propelled the blood into the relaxing heart with so much force that a large impact resulted. In a case of constrictive pericarditis, also with high venous pressure, a large diastolic complex was seen, and it proved to be simultaneous with the collapse of the venous pulse recorded optically on the same film, so evidently the same explanation holds.

In a case of aortic regurgitation, demonstrated at autopsy, the large diastolic wave was doubtless due to blood running back into the heart during diastole. Indeed, most of the abnormalities of ballistic form have physiologic explanations which seem satisfactory enough.

An abnormality of form, absent in the record taken at rest, may be easily demonstrable after exercise. Figures 2-f and g give examples of this and the explanation seems obvious; a slightly diseased heart, able to expel the blood normally during rest, is unable to do so when extra work is demanded of it.

Not so easily explained are 2 observations associated with the standing position. Certain small deviations are judged abnormal in records secured in subjects in the horizontal position because they are never found when the subject is healthy. But similar deviations are found frequently in records taken in healthy subjects standing upright (Fig. 1-f) and so these deviations cannot be regarded as abnormal in standing subjects. Indeed a healthy subject giving a normal record when horizontal may show these deviations after he arises. The reason for this is far from clear to us. Perhaps asynchronism of ejection of the 2 sides of the heart, suggested by observation made by aorta and pulmonary artery by the electrokymograph,¹ is the explanation. Such asynchronism, were it present only in the upright position, would explain our findings.

We were also surprised to find that many patients, giving abnormal records at rest, gave records more normal in form after they arose and stood upright. An example is given in Figure 2-d and 2-e. Though another explanation was considered,⁹ it is simpler to assume that this finding occurs in persons whose cardiac output diminishes on assuming the standing position, a change which relieves the heart of strain, so that in the upright position less blood needs be ejected and a weakened heart can do this in a more normal manner.

The relationship between the abnormalities of form of the ballistocardiogram, and those of the electrocardiogram deserves some further discussion. The major abnormalities of rhythm, such as auricular fibrillation, flutter and block, are usually accompanied by ballistocardiogram S abnormal in form. But it must be emphasized that the electrocardiogram and the ballistocardiogram detect abnormalities of a very different kind which are often, but need not be always, associated. Thus auricular fibrillation accompanied by ballistocardiograms entirely normal in form is not uncommon,

an indication that despite an abnormality of excitation the ventricle may still expel blood normally.

The significance of the cardiac abnormality identified by ballistocardiograms abnormal in form can best be presented by a crude example. The senior author once watched 2 men engaged in lifting a series of heavy milk cans from the ground onto a truck. The cans were lifted one at a time, each man working without assistance, and 1 workman followed the other at regular intervals until the truck was loaded. Therefore, the physical work performed by the 2 men in loading the truck was equal; it could be calculated from the product of the weight lifted and the distance it was raised. But the manner in which the 2 men performed their task was very different. One of them, a young and powerful person, raised his cans with a quick heave, while the other, an older and slighter man raised his far more slowly. The difference lay in the time required to do the lifting; the younger man could have lifted 2 cans in the time the older man took for 1. To use the terminology of the physicists, the younger man had more power.

Similarly, when the heart accelerates the blood so that maximum velocity is reached early in systole it is demonstrating more power than if the blood is accelerated more slowly, though the cardiac output may be the same in the 2 instances. Indeed, our results provide evidence that a weakening heart saves itself by lifting its load more slowly, just as a weakening man would tend to do.

Finally, we must point out the relationship between this physiologic abnormality of the heart detected by changes in form of the ballistocardiogram and that identified by one of the very oldest of clinical examinations, the palpation of the pulse. The abrupt pressure change which is detected as a strong pulse has its genesis in the rapid acceleration of the blood by the heart, and the more gradual change char-

acteristic of a soft pulse has its origin in a slower acceleration of blood. But peripheral factors also enter into the form of the pulse wave. And we believe that no clinician, however skilled, could deduce from palpation or record of the pulse, the many abnormalities so easily detected by the ballistocardiogram.

Summary. Ballistocardiograms abnormal in form have been encountered in 234 cases, of which 40 came to necropsy, during the past 10 years. The ballistic, clinical and necropsy records of these cases have been compared and the results analyzed.

The various types of abnormalities of ballistic form are described. This form may vary from beat to beat, or it may vary with respiration so that in many cases no one type of complex predominates. In other cases 1 type of abnormality does predominate, but there is usually some beat to beat variation.

Abnormalities of ballistic form were encountered most frequently in the cases in which there was manifold evidence of heart disease, or in conditions such as hypertension and hyperthyroidism in which heart disease is a frequent complication. They were found with great frequency in cases in which structural abnormalities of the heart were later demonstrated at necropsy. Nevertheless, ballistic abnormalities of form were encountered in 58 cases in which no cardiac abnormality had been suspected, and in 8 cases in which the heart was essentially normal at necropsy.

It is concluded that an abnormality of ballistic form indicates an important type of cardiac dysfunction, the manifestation of an abnormal manner of contraction. This functional abnormality is usually associated with well-known kinds of structural abnormality, but it has also been found quite frequently when cardiac disease was not detected by the routine clinical tests now in use.

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A COMPARATIVE EVALUATION OF TETRAETHYLAMMONIUM CHLORIDE AND SODIUM AMYTAL IN PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE*

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IN 1945 Acheson and Moe¹ described the pharmacologic action of tetraethylammonium, a quaternary ammonium ion, which blocks the transmission of post-ganglionic nerve impulses at the sympathetic ganglia. This temporary paralysis blocks vasoconstrictor impulses and results in a drop in blood pressure. It appears, therefore, that tetraethylammonium chloride has a specific action^{2,3,10} on the same structures, which are removed in the operative procedure known as thoracolumbar sympathectomy.

An opportunity arose to study the effect of this drug† on a sizable number of hypertensive cases. The same cases were also subjected to the sodium amytal test.

The use of sodium amytal is a fairly standard procedure in evaluation of hypertensive subjects.⁸ The test⁴ consists in the oral administration of 3 grains of sodium amytal at hourly intervals for 3 doses. The blood pressure is taken at 30 minute intervals for 4 to 6 hours.

Sodium amytal lowers the blood pressure mainly by depression of the central nervous system. It depresses the vasomotor center;^{7,11} it acts on the hypothalamus;⁹ it depresses the proprioceptive mechanism regulating the vasomotor tone;⁶ and it dilates the peripheral blood vessels by direct action. Obviously, sodium amytal does not produce a specific paralyzing action on the structures re-

moved by surgery in thoracolumbar sympathectomy. It was thought, therefore, that tetraethylammonium chloride might provide a more specific and valuable test.

Technique. The technique of the tetraethylammonium chloride test is as follows: Control blood pressure readings are taken at bedrest. The arm with the lower blood pressure is used throughout the test. Two cc. (0.2 mg.) of tetraethylammonium chloride is injected slowly, intravenously, over a period of 1 to 1½ minutes. The blood pressure is taken at 30 second intervals during the injection, and at 1 minute intervals thereafter until the control level is reached. The lowest levels are reached 1 to 3 minutes after starting the injection. In almost every case a secondary drop in blood pressure occurred about 10 minutes after the injection. This was never as extensive as the primary drop.

A comparison in the same patient between the tetraethylammonium chloride and the sodium amytal tests is shown in Figure 1. It is drawn on a semilogarithmic scale which progressively reduces the hourly intervals. The tests were performed on following days. The control blood pressure was 200/135 in both tests. During the sodium amytal test, the lowest level (160/110) was reached after 90 minutes. In contrast, only 3 minutes after the administration of tetraethylammonium chloride the blood pressure dropped to the same level. The tetraethylammonium

* A preliminary report of this study was presented at a meeting of the New York Heart Association, April 14, 1947.

† Supplied by Parke Davis & Company.

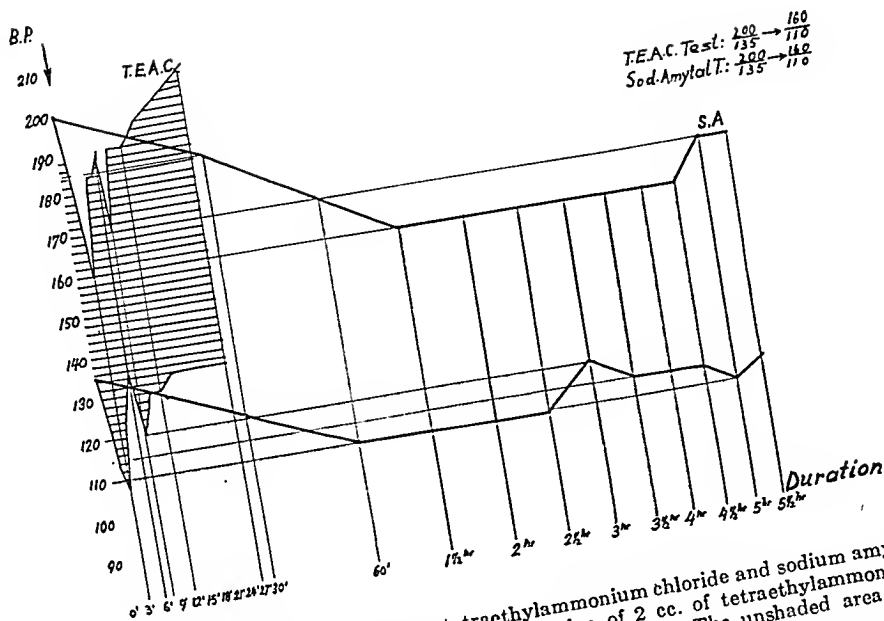


FIG. 1.—Graphic comparison between the tetraethylammonium chloride and sodium amytal test. The arrow indicates the beginning of the intravenous injection of 2 cc. of tetraethylammonium chloride. The shaded area refers to the tetraethylammonium chloride test. The unshaded area refers to the sodium amytal test.

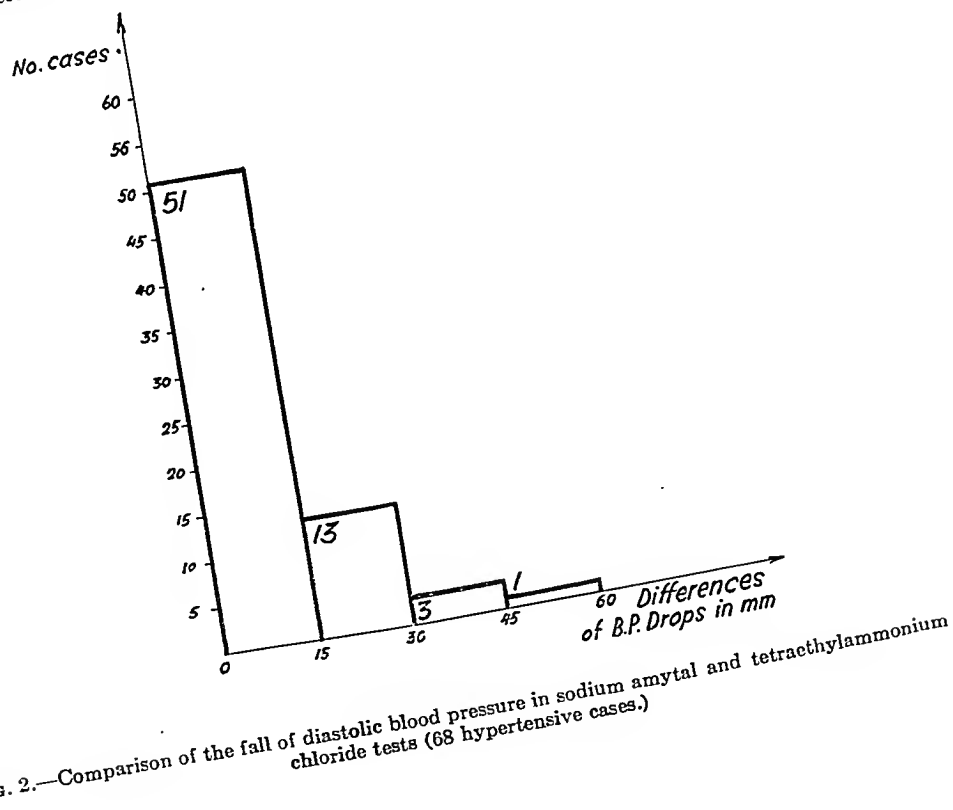


FIG. 2.—Comparison of the fall of diastolic blood pressure in sodium amytal and tetraethylammonium chloride tests (68 hypertensive cases.)

chloride test was completed in 27 minutes, while the sodium amytal test required 5½ hours.

Results. In 68 hypertensive cases the tetraethylammonium chloride and sodium amytal tests were compared. All blood pressure readings were taken by a competent and experienced nurse technician. A marked parallelism in both the systolic and diastolic drops was observed.⁵ In the following discussion, reference will be made only to the diastolic blood pressure.

diastolic fall during the tetraethylammonium chloride test of 75 to 90 mm., while the level dropped only 30 to 40 mm. during the sodium amytal test. The first 2 cases showed evidence of mild circulatory distress following the administration of tetraethylammonium chloride. A similar reaction was observed by Lyons and Moe in patients with malignant hypertension.¹⁰ The 4th case showed a more extensive drop in diastolic level during the sodium amytal test than during the tetra-

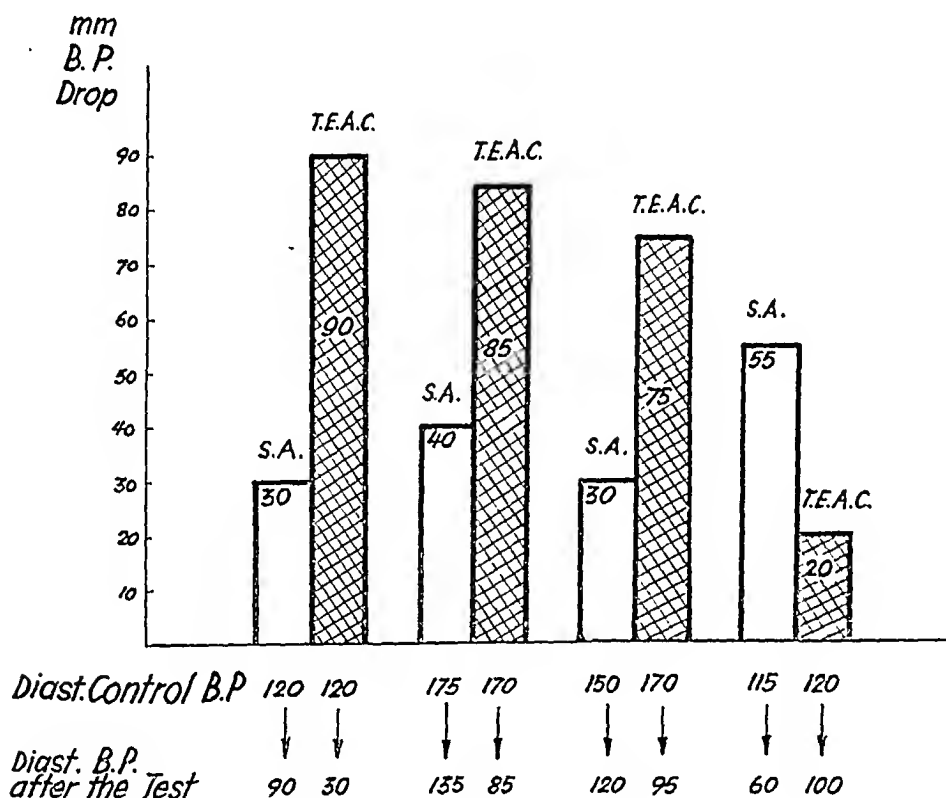


FIG. 3.—Four cases showing a marked discrepancy in the fall in diastolic blood pressure between the sodium amytal and the tetraethylammonium chloride test.

Comparing the differences between the control and lowest diastolic levels obtained during the sodium amytal tests with those obtained following the administration of tetraethylammonium chloride, it was found that these drops varied by less than 15 mm. in 51 cases, by 15 to 30 mm. in 13 cases, and above 30 mm. in 4 cases (Fig. 2).

Figure 3 shows the 4 cases in which there was a marked discrepancy between the 2 tests. In the first 3 cases, the diagnosis was malignant hypertension. These showed a

ethylammonium chloride test. In this case, the intravenous injection of tetraethylammonium chloride was painful because of poor technique. Perhaps the blood pressure failed to drop because of increased amounts of circulating epinephrine, secondary to the pain of the injection.

In our experience, side reactions to the tetraethylammonium chloride have been insignificant. They consisted in immediate tingling sensations in the extremities and tongue, and lasted only a few minutes.

Transient dizziness and weakness, pallor and visible perspiration were noted in 2 patients with malignant hypertension.

Electrocardiograms were not altered during the tetraethylammonium chloride or sodium amytal tests.

Discussion. Tetraethylammonium chloride as compared with sodium amytal appears to be a safe and more specific agent for the preoperative evaluation of hypertensive patients. Results are obtained within 30 minutes, as compared to

5 hours with sodium amytal. The patient is awake throughout the test, as compared to a day of drowsiness from sodium amytal. There is a marked parallelism in the drop in blood pressure in both tests. A study of the correlation between the 2 tests from the prognostic point of view is in progress.

Summary. The effect of sodium amytal and tetraethylammonium chloride was studied on 68 hypertensive patients and a marked parallelism in the drop of blood pressure was observed in both tests.

The authors wish to thank Dr. J. W. Hinton for the use of his cases, and Miss A. M. Mager for technical assistance.

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"CAPILLARY FRAGILITY" IN HYPERTENSION: THE EFFECT OF ANTISCORBUTIC THERAPY ON RESULTS OF TESTS FOR "CAPILLARY FRAGILITY"

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THE hemorrhagic complications of hypertension are well known to physicians and unfortunately are both known and feared by individuals with hypertension. Any method of study which is capable of predicting such a development is worthy of becoming a routine procedure in the study of hypertensive patients. The evaluation of results of prophylactic treatment, if available, would then rest on a firm basis. It has recently been suggested by Griffith and Lindauer⁴ that there is a close association between capillary hemorrhages and cerebral apoplexy. In fact, they go so far as to say that "persons with increased capillary fragility are especially predisposed to apoplexy, retinal hemorrhages and death."⁴

Previous studies had been made of the association of these 2 phenomena by Weismann,⁸ Levrat and Ballinet,⁶ Beaser, Rudy and Seligman,¹ and others. Marked differences in results were obtained which depended apparently on the technique used in performing the so-called capillary fragility test. Levrat and Ballinet obtained 85% positive reactors using a supra-diastolic positive pressure technique, and Griffith and Lindauer obtained 18% positive reactors using an infradiastolic positive pressure technique. It is interesting to note that neither of these percentages is similar to those usually reported of the number of hypertensives who suffer a cerebral hemorrhage.

Obviously, such differences in results suggest that the different techniques may be testing different functions relating to subcutaneous petechial hemorrhages, any

one of which, or any combination of which, or all of which, may not be related to the cerebral hemorrhage of hypertension. Many of the former investigators have already discussed various aspects of the significance of different techniques. The test can, of course, be performed at such a low positive pressure as to produce 100% negative reactions, and it may be possible to perform the test at such a high pressure as to obtain 100% positive reactions. It is also known that there is no relationship between the positive pressure technique and the negative pressure (suction) technique.²

Göthlin³ had already developed an infradiastolic positive pressure test for subclinical scurvy. Griffith and Lindauer used this test for capillary fragility in hypertension. It is well known that subclinical scurvy is present in many diseased states, and indeed may be present in the apparently healthy young adult. It appeared to us necessary to reevaluate Göthlin's procedure as a test for capillary fragility in hypertension, but only after subclinical scurvy had been excluded. The simplest way to do this is to saturate patients with vitamin C before performing the Göthlin test. It was also thought desirable to compare the Göthlin reaction with the Rumpel-Leede^{5,7} reaction.

Methods and Material. A capsule containing 50 mg. of ascorbic acid, 50 mg. of niacinamide, 5 mg. of thiamin chloride and 3 mg. of riboflavin, had been given to all patients studied, 3 times daily for at least 1 month prior to the tests.

The modification of the Göthlin test sug-

gested by Griffith and Lindauer was used as the infradiastolic positive pressure technique. The readings were recorded both in daylight and with the aid of a 300 watt lamp. The supradiastolic technique used was the one ordinarily known as the Rumpel-Leede test. This is performed by inflating the blood pressure cuff to approximately 10 mm. of mercury above the diastolic pressure of the patient and keeping it inflated for 5 minutes. After deflation of the cuff and after cyanosis has disappeared, the number of petechiæ present in a 2.5 cm. square area, 4 cm. below the crease of the elbow was counted. Any number below 20 was regarded as normal and any number above 20 was regarded as abnormal. This division into normal and abnormal reactions is generally accepted by most hematologists. The Göthlin test was performed before the Rumpel-Leede test and the Göthlin test was not repeated at intervals of less than 1 month. The Göthlin test was read both in daylight and with the aid of a 300 watt lamp and a small magnifying lens. If the Göthlin test was negative in both arms, the Rumpel-Leede test was performed immediately afterwards usually on the right arm.

Twenty-five non-hypertensive patients and 50 hypertensive patients were studied. Ten of the non-hypertensive patients were convalescing from tuberculosis at the Eagleville Sanatorium. The other 15 patients had complaints of non-infectious nature and were attending our out-patient medical clinic, or were on our medical wards. No selection of patients was made beyond the requirements that they should have been on the vitamin capsule previously described for at least 1 month and should have no acute infections. Only 1 diabetic patient was included in our control series (the reason being that our general medical clinic ordinarily refers the diabetic patients to a special clinic).

Results. Of the controls, only 1 gave a positive Göthlin and a positive Rumpel-Leede test. He was our only diabetic patient. It is possible that, if we had more diabetic patients in our control group, the number of positives might have been higher. The remaining 24 patients gave both a negative Göthlin and negative Rumpel-Leede reaction.

Fifty hypertensive patients were studied.

Most of these patients were from our medical clinic where they had been followed for several months to more than 10 years as hypertensive patients. The rest were private patients whose hypertension was likewise of years duration. The tests on the private patents were done, for the most part, while these patients were hospitalized for treatment of their hypertension or complications of hypertension, or for the evaluation of the type of treatment best suited for their hypertension. A few were studied in our office.

All of our patients had numerous blood pressure readings during months or years.

The criterion for a diagnosis of hypertension was a diastolic blood pressure of 100 mm. of mercury or more. Only 1 patient with a diastolic blood pressure of 90 mm. of mercury was accepted. He had consistently a systolic blood pressure above 200 mm. of mercury. All patients had eye-ground changes consistent with hypertension. Most had changes in the size and shape of the left ventricle consistent with hypertension. The blood pressure naturally varied from visit to visit but all were consistently above normal. The approximate mean blood pressures, the results of the tests of "capillary fragility" and the eye-ground findings are recorded in Table 1. It is again pointed out that all these hypertensive patients were given vitamin C and other vitamins in full dosage for at least 1 month before testing.

Discussion. It can be seen that only 2 patients, L. L. (5) and N. P. (24), gave a positive Göthlin test. L. L. had Paget's disease and N. P. had diabetes. Thirty-three patients (66%) gave a positive Rumpel-Leede test. The 2 with a positive Göthlin reaction had a mild type of hypertension. Although the Rumpel-Leede test appears to be more frequently positive as the diastolic pressure increases, there is no absolute correlation between the diastolic blood pressure and a positive Rumpel-Leede reaction, as occasionally the Rumpel-Leede test is positive with a

TABLE 1.—DATA ON CAPILLARY FRAGILITY, EYEGROUNDS AND BLOOD PRESSURE IN 50 HYPERTENSIVE PATIENTS WHO HAD RECEIVED VITAMIN C IN FULL DOSES FOR 1 MONTH OR MORE

		No. petechiae						
		Gothlin 300 w. lamp and daylight Arms (6 cm. sq.)				Rumpel-Leede Arm (2.5 cm. sq.)		
Name	Age	Blood pressure	R	L	R	L	R	Eye-grounds, grade of sclerosis and remarks
1. L. B.	79	212/90	0	0	0	0	70	ii
2. M. C.	60	206/100	0	0	0	0	0	Marked angiospasm
3. B. L.	37	160/100	0	0	0	0	42	i
4. V. T.	39	130/100	—	—	0	0	0	ii
5. L. L.	59	150/100	—	—	6	7	Countless	i and Paget's disease
6. H. B.	49	165/105	1	1	1	1	30	i
7. R. B.	47	170/105	1	1	1	1	35	i
8. G. E.	48	150/100	0	0	0	0	0	i
9. G. O.	48	152/104	0	0	0	0	0	i
10. G. S.	38	140/100	0	0	0	2	50	i and pulmonary tuberculosis
11. S. A.	52	150/100	0	0	0	0	0	i
12. M. W.	58	170/100	0	0	0	0	0	i
13. E. W.	62	170/102	0	0	0	0	34	i
14. D. K.	48	165/105	0	0	0	0	Countless	i
15. D. S.	53	170/100	0	0	0	0	Countless	i and goiter and anemia
16. J. C.	50	170/100	0	0	0	0	10	ii
17. M. B.	47	170/110	1	0	0	0	60	i
18. T. T.	50	170/116	0	0	0	0	10	i
19. W. M.	63	210/110	0	0	0	0	0	ii and hemorrhages
20. R. H.	68	190/110	0	0	0	0	0	i
21. M. P.	45	190/110	0	0	0	0	60	i
22. C. S.	62	240/110	0	0	1	1	4	i
23. E. E.	62	170/115	2	1	0	1	40	ii
24. N. P.	58	178/118	—	—	5	7	Countless	i and diabetes
25. S. L.	63	210/120	0	0	0	0	15	ii and coronary artery disease
26. E. H.	60	195/120	1	2	1	1	50	ii
27. M. T.	46	220/120	0	0	0	0	0	ii
28. R. C.	37	160/120	0	0	0	0	42	i
29. H. S.	54	200/120	1	0	0	1	21	i
30. F. G.	52	226/120	0	0	0	0	7	i
31. T. L.	54	218/120	1	0	0	0	21	i
32. F. R.	54	210/120	1	1	0	0	Countless	ii and apoplexy
33. G. D.	41	175/118	—	—	0	1	Countless	i
34. G. P.	17	190/130	1	0	0	0	59	ii
35. C. S.	54	224/130	0	1	0	0	100	ii
36. E. D.	52	226/120	0	0	0	0	100	iii
37. K. S.	42	220/130	—	—	0	1	Countless	ii and hemorrhages
38. M. R.	36	170/128	—	—	0	2	Countless	ii and hemorrhages
39. C. K.	57	185/125	—	—	1	1	Countless	ii and hemorrhages
40. G. R.	47	200/130	—	—	1	1	Countless	ii and diabetes
41. S. D.	44	160/120	0	0	0	0	Countless	Angiospasm
42. E. H.	44	232/128	0	0	0	0	0	Retinitis of malignant hyper- tension
43. J. B.	52	176/120	0	0	0	0	50	iii and hemorrhages
44. M. G.	37	230/140	—	—	0	0	Countless	ii and hemorrhages
45. K. S.	42	240/150	—	—	1	1	Countless	iii and hemorrhages
46. R. S.	27	240/140	—	—	1	1	Countless	ii and hemorrhages
47. Y. F.	29	196/140	0	1	0	0	60	i
48. L. F.	49	230/150	0	0	0	0	6	i
49. P. T.	60	250/150	—	—	0	—	21	Severe angiospasm
50. A. B.	39	260/170	0	0	0	0	4	Retinitis of malignant hyper- tension

TABLE 2.—THE EFFECT OF RUTIN ON THE GÖTHLIN AND RUMPEL-LEEDS REACTIONS OF HYPERTENSIVE PATIENTS PREVIOUSLY SATURATED WITH VITAMIN C

Names	Before rutin therapy and after at least a month of vitamin C therapy		After 1 mo. of rutin and 2 mo. of vitamin C therapy	
	(No. of petechiae)		(No. of petechiae)	
	Göthlin	Rumpel-Leede	Göthlin	Rumpel-Leede
5. L. L.	13	Countless	10	Countless
10. G. S.	2	50 or more	..	50 or more
15. D. S.	0	Countless	..	Countless
17. M. B.	0	50 or more	..	50 or more
21. M. P.	0	50 or more	..	50 or more
24. N. P.	12	Countless	9	Countless
26. E. H.	2	50 or more	..	50 or more
32. F. R.	0	Countless	..	Countless
33. G. D.	1	Countless	..	Countless
34. G. P.	0	50 or more	..	50 or more

It is seen from these results that rutin was not able to reverse the Rumpel-Leede test to normal or the 2 positive Göthlin reactions to normal in our hypertensive patients who had been previously saturated with vitamin C.

minimal increase in pressure and it is rarely negative with a marked increase in pressure. It is interesting to note that the patient with the highest pressure we observed, who also had numerous retinal hemorrhages, gave a negative Rumpel-Leede test (A. B., Case 50, in a malignant phase of essential hypertension).

Age appears to be no factor in the production of a positive Rumpel-Leede test, as the average age group in each is 47 years.

It is noteworthy that 3 (19, 42, 50) of our 9 patients with retinal hemorrhages gave a negative Göthlin and Rumpel-Leede reaction. This suggests that there is no correlation between a negative Rumpel-Leede or Göthlin reaction with absence of retinal hemorrhage. There is obviously no correlation between a positive Rumpel-Leede reaction and the presence of retinal hemorrhages as over 80% of our hypertensive patients with positive Rumpel-Leede reactions had no retinal hemorrhages.

Retinal hemorrhages may be related to the diastolic blood pressure, as all our patients, with a single exception, who showed this phenomenon had a diastolic pressure above 120 mm. of mercury. This 1 exception, a 63 year old hypertensive patient, had a blood pressure of 210/110. The diastolic blood pressure, however, is not the only or the determining factor. This is indicated by the fact that 8 (50%) of our patients with a diastolic blood pressure above 120 mm. of mercury had no retinal hemorrhages.

Griffith and Lindauer⁴ found the Göthlin test positive in 18% of their hypertensive patients. We had only 2 patients (4%) with positive Göthlin tests. This may have been due to the fact that our patients had been saturated with vitamin C for at least 1 month before the Göthlin test was performed. At any rate, we could not test the effect of rutin on the Göthlin reaction except in these 2 patients.

We thought it worth while to test the effect of rutin on patients with a positive

Rumpel-Leede reaction. Ten patients were re-studied (5, 10, 15, 17, 21, 24, 26, 32, 33 and 34). The patients were kept on the vitamin capsule and in addition were given 20 mg. of rutin 3 to 4 times a day for 1 month. The Göthlin test and the Rumpel-Leede test were repeated. No significant difference in the number of petechiæ or the intensity of the petechial reaction was observed. The results are recorded in Table 2.

To us there appear to be 3 possible reasons for the negative Göthlin tests in our hypertensive patients:

1. The petechiæ may have escaped our observations. The petechiæ which appear after a positive Göthlin reaction are smaller and fainter than those after a positive Rumpel-Leede reaction. We were aware of the difference in the appearance of the petechiæ and independently examined the first 25 hypertensive patients in daylight and with a 300 watt lamp, with this thought in mind. Certainly, if the petechiæ were so small as to escape our observations, we feel that this test is not apt to be generally successful in the hands of other physicians.

2. We may have had an unusual run of negative results and our results might have been different had we continued with more patients. Although this possibility exists, it appears highly improbable.

3. The administration of vitamin C may have prevented the appearance of a positive Göthlin test. This appears to us the most likely explanation and it suggests the need for reevaluation of this test on a large series of patients previously saturated with vitamin C.

Bell, Lazarus and Munro² had already made a critical analysis of capillary fragility determined by the Göthlin method. They reported a 10.7% positive reaction in presumably healthy normal students of 20 years of age living on a diet which was available in England in 1940. All but 2.5% responded to vitamin C. They also noticed variations with light intensity, season and menstrual cycle. It is possible

that hypertensive patients have a higher incidence of subclinical scurvy than the normal students studied by Bell, Lazarus and Munro.

Conclusions. 1. The capillary fragility of 50 hypertensive patients previously saturated with vitamin C for 1 month, was determined by the Göthlin and Rumpel-Leede tests.

2. Only 2 patients had a positive Göthlin test and 33 had a positive Rumpel-Leede test.

3. When the Göthlin test was performed on hypertensive patients previously placed on an adequate vitamin C intake, we were unable to verify the results obtained by Griffith and Lindauer.

4. Rutin did not reverse to normal the Göthlin test of 2 patients who had been previously saturated with vitamin C.

5. Rutin did not reverse to normal the Rumpel-Leede test.

6. There does not appear to be any correlation between retinal hemorrhages and a positive Rumpel-Leede reaction.

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THE RELATIONSHIP OF RETINAL HEMORRHAGES IN HYPERTENSIVE PATIENTS TO CEREBRAL HEMORRHAGE

A COMPARISON OF THE RETINAL PICTURE IN HYPERTENSIVE INDIVIDUALS WHO DIED OF HEART FAILURE WITH THOSE WHO SUFFERED A CEREBRAL HEMORRHAGE

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CEREBRAL hemorrhage is said to be the cause of death in a little less than one-third of all hypertensive individuals. Conversely, hypertension is present in well over 90% of individuals dying of cerebral hemorrhage. In spite of the frequency of cerebral hemorrhage, the pathogenesis of this accident in the hypertensive patient is still obscure. Two factors appear to be operative. One is hypertension or sudden variations in hypertension. The other is apparently a local factor, as it is well known that extremely high pressures such as are not present during life, fail to produce hemorrhage in the brain of cadavers. Various local factors have been invoked. Charcot and Bouchard¹ thought that miliary aneurysms were present which ruptured under a sudden increase in pressure. Rosenblath⁴ suggested a hypothetical enzyme of renal origin which produced destruction of nerve tissue. Westphal and Bar⁵ suggested repeated angiospasm which produced ischemia of nerve tissue and thereby weakened the support of blood-vessels as they reopened. Globus and Strauss² suggested an ischemic necrosis of nerve tissue due to progressive arteriolar sclerosis and obliteration of the lumina of the cerebral vessels. This weakened the support of the walls of the blood-vessels as they dilated under the influence of a sudden increase in the pressure. Scheinker³ was impressed by the rich ven-

ous system of those regions of the brain stem which are commonly the seat of massive hemorrhage. He was also impressed by the lack of hemorrhage in those regions which are rich in arterial and capillary network. He described stasis, distention, atrophy, degeneration, occlusion and necrosis of veins in the regions of hemorrhage and he believes that the hemorrhage is of venous rather than arterial origin. Recently, Griffith and Lindauer³ suggested the frequent association of capillary hemorrhage, retinal hemorrhage, cerebral hemorrhage and death in hypertensive individuals. Retinal hemorrhages are readily accessible to inspection. We therefore decided to try to estimate the value of retinal hemorrhage as a prognostic sign of cerebral apoplexy.

Method and Material. The records of all patients with hypertension who had been admitted to Temple University Hospital between 1941 and 1946 inclusive and had died or had sustained a cerebral hemorrhage were reviewed. Only those records which contained an eye-ground study made by Dr. Walter I. Lillie or Dr. Glenn G. Gibson of the Department of Ophthalmology of Temple University Medical School were accepted for study. This was done so that there would be no question about the examination or interpretation of the retinal picture. Both these ophthalmologists are intensely interested in the retinal picture of hypertension and follow the classification advocated by Wagener of the Mayo Clinic.

Here, in brief, the term attenuation refers to a generalized uniform narrowing of the arterioles. Angiospasm refers to areas of marked prolonged narrowing in the course of an attenuated arteriole. Sclerosis is graded from 1 to 4, depending upon the degree of irregularity of the lumen and the smallness of the caliber of the arteriole. Severe angiospasm may produce retinitis characterized by edema of the disk and hemorrhages and exudates. The malignant phase of hypertension is characterized by edema of the disk, hemorrhages, exudates and sclerosis of the arterioles.

50 years. The average age is not apparently lowered by including 1 patient with glomerulonephritis. There were 6 males among the group with cerebral hemorrhage and 5 males among the group with heart failure and no cerebral hemorrhage. Those with cerebral hemorrhage had a systolic pressure varying from 150 mm. of mercury to 240 mm. of mercury and a diastolic pressure from 90 to 150 mm. of mercury with an average pressure of 190/113. Those with heart failure had a systolic pressure varying from 150 to 260 mm. of mercury and a diastolic pressure varying from 90 to 160 mm. of mercury with

TABLE 1.—DATA OF 5 HYPERTENSIVE PATIENTS WITH CEREBRAL HEMORRHAGE AND WITH RETINAL HEMORRHAGES

Name	Age	Sex	Blood pressure	Blood urea	Eye-grounds	
					Grade of sclerosis	Hemorrhages
B	63	F	240/118	22.9	ii	Yes
S	60	M	220/110	20.0	Spasm	Yes
D	49	F	210/130	..	ii (malignant hypertension)	Yes
B	42	F	180/130	18.0	ii	Yes
T	64	M	190/110	..	ii	Yes

All patients had had hypertension for months or years. The diastolic blood pressure was constantly 100 mm. of mercury or more in all patients except 3 who had terminal drops in pressures: 1 to 90 mm., 1 to 98 mm. and the other who during terminal shock had a pressure of 138/88. The lowest pressures of these 3 individuals are recorded. The mean blood pressures of the other patients are recorded. There were 18 patients who died of cardiac failure. The diagnosis of cardiac failure was based on the classical findings of an enlarged heart, pulmonary congestion, dyspnea, edema of the lower extremities, enlarged liver and previous partial response to digitalis and diuretics. There were 17 hypertensive patients who had sustained a massive cerebral hemorrhage. This diagnosis was confirmed in all cases by members of the Department of Neurology. The diagnosis was confirmed furthermore in 4 cases by autopsy, in 6 cases by frank bloody spinal fluid and in the other 7 by rapid progressive neurologic changes indicating a space-taking lesion.

Those with cerebral hemorrhage varied in age between 42 years and 76 years with an average of 66 years. Those with heart failure without cerebral hemorrhage varied in age from 17 years to 78 years with an average of

an average pressure of 199/126. In only 1 patient with cerebral hemorrhage was the blood urea nitrogen recorded as above normal (87 mg. per 100 cc. of blood), whereas in the cardiac group 11 patients had blood urea nitrogen varying from 40 to 195 mg. per 100 cc. of blood. There is no significant difference in the sex incidence in the 2 groups. There is a slight increase in the mean diastolic blood pressure of the cardiac failure group. The cardiac failure group has a decided increase in percentage of patients with renal functional impairment. The cerebral accident group is significantly older (an average of 16 years).

Eye-ground Findings. Of the 17 patients who suffered a cerebral hemorrhage, 5 (29.4%) had retinal hemorrhages. Of these 5 patients, 1 had the malignant phase of hypertension with a grade ii sclerosis, 3 had grade ii arteriosclerosis and the fifth had regions of spasm (see Table 1). Twelve (70.6%) had no retinal hemorrhages. Of the 12 cases of cerebral hemorrhage without retinal hemorrhage, 2 had attenuation (generalized narrowing of the arterial tree), 5 grade i sclerosis, 4 grade ii sclerosis and 1 showed no evi-

dence of hypertension (see Table 2).

Of the 18 hypertensive patients who died of heart failure and had no cerebral accident, 14 (77.7%) had retinal hemorrhages. Of these 14 patients, 4 had grade iii sclerosis with spasm, 7 had grade ii sclerosis with spasm and the other 3 had large regions of spasm (see Table 3). The 4 without retinal hemorrhages had grade ii sclerosis. There was

Discussion. The number of cases studied is obviously too small to draw unquestionable conclusions. Although our results show a difference in the 2 groups of more than 3 times the standard error, yet the number of cases is too small for valid statistical analysis. We could have increased the number of cases several fold had we included the patients whose eye-grounds had not been examined by

TABLE 2.—DATA OF 12 HYPERTENSIVE PATIENTS WITH CEREBRAL HEMORRHAGE BUT WITHOUT RETINAL HEMORRHAGES

Name	Age	Sex	Blood pressure	Blood urea	Eye-grounds	
					Grade of sclerosis	Hemorrhages
G	55	M	172/120	24.0	ii	None
S	63	F	210/150	17.2	Attenuation	None
C	63	F	180/100	..	i+	None
B	54	F	168/110	15.0	ii	None
P	70	F	180/120	20.0	ii	None
F	65	M	168/98	18.5	i	None
G	58	F	168/110	..	i	None
H	55	M	212/110	16.0	i	None
R	56	F	170/110	..	Attenuation	None
N	76	M	150/90	22.0	i	None
O	52	F	138/88	19.0	None	None
			(shock)	87.0	ii	None
S	38	F	220/115	87.0	ii	None

TABLE 3.—DATA OF 14 HYPERTENSIVE PATIENTS WITH CARDIAC FAILURE WITHOUT CEREBRAL HEMORRHAGE BUT WITH RETINAL HEMORRHAGES

Name	Age	Sex	Blood pressure	Blood urea	Eye-grounds	
					Grade of sclerosis	Hemorrhages
A	54	F	210/130	..	ii*	Yes
P	53	M	240/144	96.5	iii*	Yes
P	49	F	182/100	195.0	ii*	Yes
K	48	F	240/100	40.0	ii*	Yes
L	48	F	216/130	44.0	Spasm	Yes
M	35	F	210/160	138.0	ii*	Yes
C	17	F	162/112	93.0	Spasm	Yes
J	59	M	228/140	57.0	ii*	Yes
K	61	F	150/90	105.0	ii*	Yes
T	41	F	210/130	75.0	Spasm	Yes
L	45	F	260/150	..	iii*	Yes
P	74	F	210/148	94.5	ii*	Yes
R	42	M	160/120	..	iii*	Yes
J	38	M	170/130	124.0	iii*	Yes

* With spasm.

no significant difference in the range of blood pressure of those with retinal hemorrhages and those without retinal hemorrhages either in the cerebral hemorrhage group or the cardiac failure group (see Table 4).

Our findings are summarized in Table 5.

ophthalmologists. Several of us in the Department of Medicine have followed for years the methods recommended by the Department of Ophthalmology and we feel confident in our ability to see and interpret the retinal picture in hypertension. Had these cases been included, the

results would have been similar, but then objections might have been raised concerning the interpretation of the eye-grounds which were not examined by ophthalmologists.

The trend, however, even with this small group, appears to be definite. The finding of retinal hemorrhages in 29.4% of the cerebrovascular hemorrhage group and in 77.7% of the group dying of cardiac failure without cerebral hemorrhage, even

Lillie and Gibson in 42 consecutive hypertensive patients who were admitted to Temple University Hospital for study. This group had neither heart failure nor a cerebral accident. The data are summarized in Table 6.

Of these 42 hypertensive patients without a cerebral accident or cardiac failure, 10 had retinal hemorrhages. The presence or absence of retinal hemorrhages had no relationship to age, sex or blood pressure.

TABLE 4.—DATA OF 4 HYPERTENSIVE PATIENTS WITH CARDIAC FAILURE WITHOUT CEREBRAL HEMORRHAGE AND WITHOUT RETINAL HEMORRHAGES

Name	Age	Sex	Blood pressure	Blood urea	Eye-grounds	
					Grade of sclerosis	Hemorrhages
S	55	F	170/130	..	ii	None
G	53	F	212/110	45	ii	None
F	54	M	220/142	..	ii	None
G	78	F	150/100	38	ii	None

TABLE 5.—SUMMARY OF CERTAIN CLINICAL DATA, NOTABLY RETINAL AND CEREBRAL HEMORRHAGES, IN 35 PATIENTS WITH HYPERTENSION

	Cerebral hemorrhage	No cerebral hemorrhage
Retinal hemorrhages	5	14
No retinal hemorrhages	12	4
Mean age	66 years	50 years
Mean blood pressure	190/113	199/126
Increase in blood urea nitrogen	1 (0.59%)	11 (61.1%)

though the cerebrovascular group averaged 16 years older than the heart failure group, indicates that retinal hemorrhages cannot be used as a sign prophetic of future massive cerebral hemorrhage. Indeed, the reverse appears true: namely, that a hypertensive patient with retinal hemorrhages has a greater chance of dying of cardiac or renal failure. It would appear from this study that retinal hemorrhages are more commonly seen in the hypertensive patients who have some evidence of uremia. The uremia may be of renal or extrarenal (cardiac failure) origin. It is seen in patients who have either at least a grade ii sclerosis with spasm or large regions of marked spasm.

In order better to determine the nature of the type of hypertension which produces retinal hemorrhages, we analyzed the eye-ground findings observed by Drs.

Of the 10 retinal hemorrhages, 3 had large regions of spasm and attenuation. Three had grade iii sclerosis with spasm. Two had grade ii sclerosis with spasm. Two had grade i sclerosis with marked spasm. Of those without hemorrhages, 4 had attenuation, 19 grade i sclerosis (including 1+ sclerosis), 7 grade ii sclerosis (including ii+ sclerosis), 1 had grade i sclerosis with spasm, and 1 had negative eye-grounds. This analysis tends to confirm that of the previous groups. A marked degree of spasm usually with grade ii sclerosis is necessary for the production of retinal hemorrhages. The spasm is apparently of importance in producing an extra burden on the heart or kidneys and thereby producing failure of either or both these organs. Apparently, if this is not correctable, the patient does not live long enough to suffer a cerebral accident.

Summary and Conclusions. 1. Retinal hemorrhages occurred in 14 (77%) of 18 patients with hypertension who died of cardiac failure without cerebral hemorrhage.

2. Retinal hemorrhages occurred in 5 (29%) of 17 patients with hypertension who suffered a cerebral hemorrhage.

3. Retinal hemorrhages occurred in

hypertensive patients who had large regions of spasm with or without a grade ii sclerosis.

4. Retinal hemorrhages cannot be used as a prognostic sign of future cerebral hemorrhage, as they occur more frequently in those who ultimately die of cardiac or renal failure without a massive cerebral accident.

TABLE 6.—CLINICAL AND OCULAR FINDINGS IN 42 HYPERTENSIVE PATIENTS WITHOUT CEREBRAL ACCIDENT OR CARDIAC FAILURE

Name	Age	Sex	Blood pressure	Eye-grounds	
				Grade of sclerosis	Hemorrhages
R	45	F	180/130	i	None
M	28	F	160/112	ii	None
B	58	M	190/90	i	None
M	49	F	168/110	i*	None
Z	43	F	196/104	ii	None
G	49	M	214/140	i+	None
S	50	M	237/120	i+	None
K	64	F	180/130	i+	None
E	62	F	174/110	i	None
T	42	F	174/115	i	None
W	40	F	210/150	i	None
O	41	F	194/94	i+	None
G	31	M	170/114	Attenuation*	Yes
M	50	M	172/110	ii	None
R	47	F	182/120	i	None
D	42	F	170/92	iii*	Yes
S	43	M	170/108	i+	None
K	45	M	200/154	ii*	Yes
U	50	F	240/130	i	None
B	48	M	240/120	Attenuation	None
G	39	M	228/160	iii*	Yes
F	64	F	224/96	i	None
P	53	M	222/122	i+	None
D	54	F	160/90	ii	None
K	26	F	136/88	Attenuation	None
G	28	M	140/100	None	None
G	30	M	234/138	ii+	None
S	35	M	150/100	i	None
S	50	F	200/120	i	None
H	16	F	200/150	Attenuation*	Yes
W	57	M	204/132	Attenuation*	Yes
S	48	M	180/150	i	None
S	54	M	138/98	i*	Yes
W	43	F	150/90	ii	None
A	44	M	258/150	Attenuation	None
H	41	F	188/110	ii	None
W	31	F	180/120	i*	Yes
A	30	F	188/110	i	None
S	55	F	212/110	i	None
F	52	M	230/128	ii*	Yes
T	50	M	140/100	Attenuation	None
H	77	F	184/110	iii*	Yes

* Spasm.

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BRONCHOPULMONARY HYPOGENESIS

Clinical and Roentgenologic Features in the Adult, with long Follow up Observations.

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UNTIL now, less than 60 cases of agenesis or aplasia of the lungs have been reported,³ the majority of these having been seen in infancy and early childhood. The congenital anomalies of the lower respiratory tract may vary from complete absence of both lungs, as described in Schmitt's case,⁹ to the presence of a partially developed bronchopulmonary system on one side and normal lung and bronchi on the other. The latter condition, bronchopulmonary hypogenesis, has until now been encountered far less frequently in the literature than agenesis. However, with the continued extension of chest Roentgen ray surveys throughout the country among apparently normal adult groups, it is likely that cases of hypogenesis will be uncovered that would otherwise go unrecognized. The reason for this lack of recognition is because the condition is more compatible with asymptomatic living than are those with complete absence of 1 lung.

Faulty development of the lung on one side is an accident of nature which has taken place early in fetal life, well before the fetus is 3 months old.^{1,7} Patients exhibiting this developmental error frequently display evidence of other anomalies in the tracheobronchial tree, as well as elsewhere in the body.^{2,5} Unlike cases of atelectasis of the newborn, patients with bronchopulmonary hypogenesis show lack of respiratory difficulty at birth,¹³ indicating that the anomaly has had time *in utero* for compensation by hypertrophy of the remaining lung tissue. Likewise, external symmetry of the chest is maintained in most cases, or only slightly altered,^{4,12} because the potential space is filled by displaced mediastinal contents

and a portion of hypertrophied contralateral lung at an early stage of development.

A youngster with agenesis or hypogenesis of the lung will often come to the early attention of the pediatrician or the radiologist, as in the first case described below, during an attack of bronchopneumonia to which these patients fall an easy prey.⁶ Later in life, individuals with this anomaly may complain of frequent colds, dyspnea on slight exertion, expectoration of blood-streaked sputum or even frank blood, and attacks of stertorous or wheezy breathing; the latter, too, may be the only, albeit distressing, clinical feature early in life.⁸

To diagnose this condition in the adult, its possibility must be thought of when a chest radiograph shows diffuse clouding on one side with retraction of the heart and mediastinum well over to that area. In recent years, with the increased use of the bronchoscope and especially the bronchogram, the correct underlying pathology has been more frequently established during life, than was the case over a decade ago, when the presence of congenital bronchopulmonary anomalies was mostly an autopsy finding. The chief difficulty has been to distinguish agenesis or hypogenesis of the lung from the end-results of primary tuberculosis or the so-called natural thoracoplasty that ensues in the fortunate healing of a diffuse unilateral reinfection pulmonary tuberculosis. It may also be mistaken for the combination of atelectasis and pulmonary fibrosis associated with obstructive benign tumor of the bronchus. Suspicion of the latter would naturally lead to operation.¹¹

The writer's attention was recently

called to the case of a young woman who complained of dyspnea and blood-spitting of 10 years duration and had had the right lung removed because the bronchoscopist and clinician thought it to be the seat of bronchial adenoma, only to find it a mal-developed organ similar to the cases to be described. Months later, the symptoms for which she was in a sanatorium 10 years previously were still the same as before the pneumonectomy.

heart and mediastinum to the right. After the instillation of lipiodol the trachea was described as displaced to the right, with the bifurcation to the right of the thoracic spine; one collection of opaque oil was said to be at the beginning of the right upper lobe bronchus, and the other near the junction of the middle and lower lobe bronchi, and no evidence was found of bronchiectatic dilatations.

While he was at Temple University Hospital, it was determined that congenital



FIG. 1.—Case 1. Film taken in early infancy (Feb. 24, 1931) showing marked retraction of heart and mediastinum to the right; diffuse haze right lung field except costosplenic region; compensatory emphysema left lung.

Case Reports. CASE 1. J. C. is a Negro, now 18 years of age. His family history is negative except for contact with a sister who had an open case of pulmonary tuberculosis. The boy first came to us because of the exposure history. His birth history was uneventful, and he was well until 2 months of age, when hospitalization was necessary because of a severe attack of pneumonia. After a stay in a hospital in Washington, D. C., where a diagnosis of "massive atelectasis of the right lung of undetermined etiology" was made, he was transferred to Temple University Hospital to which we are indebted for reproductions of the chest films and bronchograms done in this case 18 years ago. The Wassermann test at that time was negative, and a culture of the bronchial secretions was negative for tubercle bacillus, pneumococcus or spirilla.

A Roentgen ray, taken on Feb. 24, 1931 (Fig. 1), was reported as showing some abnormal density throughout the right side of the chest, with marked displacement of

dextrocardia was not present. The conclusion before discharge at that time was that all the chest findings could be explained on the basis of atelectasis of the right lung.

This boy has been followed by us at semi-annual intervals for the past 4 years. He has been growing normally and is apparently healthy and vigorous. His frequent efforts to enlist in the Armed Forces were halted only by the routine chest film which always thwarted this ambition. In the intervening 17 years, he has not been seriously ill. However, he has been subject to frequent colds. He is somewhat dyspneic on moderate exertion, expectorates a small amount of non-odorous sputum daily, and after many years of frequent spitting up of blood, raising at times 2 ounces of bloody sputum, he is no longer alarmed. Repeated sputum examinations have been negative for tubercle bacilli. The tuberculin test has been negative to 1 mg.

Examination of the chest has revealed only slight asymmetry of the right chest

whose respiratory excursions are diminished. There is dullness, diminished breathing and no râles over the right thorax.

The chest film taken on April 24, 1947 (Fig. 2), shows the thoracic contents to be the same as in 1931, except that there is more aëration on the right side. In passing it may be noted that an azygos fissure is seen in the left lung field, and this stands out more clearly in the adult film. A

bronchogram on this patient on May 27, 1947 (Fig. 3), reveals little difference in the bronchopulmonary abnormalities of the right side from the bronchogram of infancy, except that the hypogenetic bronchial tree is more easily traced. One sees that the trachea slants well over to the right chest. At the bifurcation, a bizarre bronchus comes off at right angles to the windpipe, and from this bronchus numerous weird branches

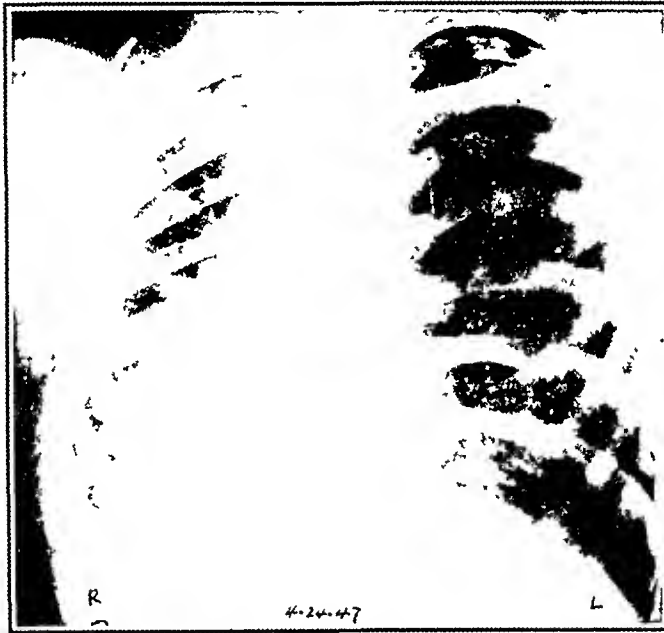


FIG. 2.—Case 1. Film taken 16 years later (April 24, 1947) showing more aeration right lung, right mediastinal border is now easily distinct. Note the left azygos tissue.



FIG. 3.—Case 1. Bronchogram done, May 24, 1947, showing bizarre single right bronchus with its weird branches and 2 additional undeveloped bronchi of the first order ending in blind sacs a short distance from their origin.

scatter throughout the apparently single-lobed right lung. Two other branches end in blind sacs a short distance from their origin. The left main bronchus can be seen crossing over from the right side.

It appears that here we are dealing with a hypogenesis of the right lung in which the radiologic and bronchographic features have shown little change in 17 years of observation.

dary anemia. During her stay at the hospital, nothing remarkable was found in the gastro-intestinal tract.

She was first seen in the Health Department Clinic on Nov. 21, 1938, for routine examination because of exposure to her brother, who died of pulmonary tuberculosis. When interviewed in our Clinic, careful questioning elicited the fact that this girl had been coughing and expectorating gritty



FIG. 4.—Case 2. Marked retraction of heart to right, baring the thoracic spine. Aërated lung is visible in right upper chest.

CASE 2. H. S. is a Negress, born on Oct. 6, 1919. At the age of 8, because of a 5 years history of epigastric distress, she was observed in the wards of Roosevelt Hospital for a period of 2 months. At that time, a routine examination of the chest revealed dullness on the entire right side, diminished breath sounds and fremitus with bronchial breathing and occasional râles and squeaks in the right chest. A chest film done on Dec. 1, 1927, showed diffuse clouding on the right side, with retraction of the heart and mediastinum well over to the right side. On fluoroscopy, the right diaphragm moved paradoxically and the mediastinal shadow shifted slightly to the left on inspiration. She was last seen at Roosevelt Hospital on Aug. 1, 1937, when a chest roentgenogram revealed nothing new. She was also found to have a well-marked second-

ary material since childhood. She has occasionally noticed a wheezy feeling and her sputum has been blood-streaked at times. Upon examination she appeared well developed and well nourished. There were essentially the same physical findings in the chest as reported at the hospital. Roentgen ray of the chest taken on Jan. 7, 1939 (Fig. 4), shows diffuse clouding of the lower two-thirds of the right thorax, with the heart well over to that side, and the trachea drawn over to the right.

A bronchogram done on the same day (Figs. 5 and 6) shows a marked narrowing at the lower end of the right main bronchus. An apparently normal branch comes off the main bronchus and is seen to arborize anteriorly and medially in the direction of the lower lung field.

Also coming off the right main bronchus are 2 branches ending in large blind sacs some distance from their origin. As in the previous case, the left main bronchus crosses over in apparently normal fashion into the left lung field. Since no bronchus is traceable to the right upper lobe, one cannot be sure from this film whether the right upper

lobe is present or whether the aerated area in the right upper lobe region is really herniated left lung.

The patient was followed by our Clinic until Jan. 6, 1945, when she stopped coming. However, a letter received from her a month ago indicated that she was enjoying good health in Southern California.



FIG. 5.—Case 2. Bronchogram (Jan. 7, 1939) shows well the narrowing of the trachea near the bifurcation. Note the normal looking bronchi going toward the right lower lung field and, more medially, the 2 other blind sacculated branches.



FIG. 6.—Case 2. Lateral view of bronchogram more clearly defining the undeveloped bronchi and their position.

Summary and Conclusions. 1. Two cases of bronchopulmonary hypogenesis followed for more than 15 years are presented.

2. It is expected that many more of these cases will be uncovered in routine chest surveys.

3. The importance of bronchographic study in making the diagnosis is emphasized.

4. Unlike those previously reported, these cases are not symptom-free, although their symptoms are not disabling.

5. Due to the wide practice of chest surgery, such patients have had unnecessary and ineffectual operations on the affected side when the presence of bronchopulmonary hypogenesis was not borne in mind.

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THE EFFECT OF EXERCISE ON THE ELECTROCARDIOGRAM (MASTER "TWO-STEP" TEST) IN THE DIAGNOSIS OF CORONARY INSUFFICIENCY

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THE diagnosis of coronary insufficiency in patients presenting a questionable or vague history of anginal syndrome but no objective evidence of heart disease is often a difficult one. Physical examination, electrocardiograms and Roentgen ray and fluoroscopic study of the heart may all be within normal limits. In this group of patients it is often desirable to obtain objective evidence of diminished coronary reserve. The anoxemia test¹⁵ standardized by Levy and his associates, and the "two-step" exercise test introduced and studied by Master *et al.*^{18,19,20} have served as diagnostic aids in this problem. The present report is concerned with an evaluation of the exercise test in the diagnosis of coronary insufficiency.

The electrocardiographic changes associated with spontaneous episodes of angina pectoris have been described by a number of observers.^{4,5,9,11,12,25,28,30,34,36,37,39} These consist generally of a depression of the *S-T* segment of one or more leads and flattening or inversion of *T* waves. Similar changes have been noted during induced attacks of angina following exercise.^{28,36,37,39} Induced anoxemia and temporary interference with the coronary circulation have been shown experimentally to produce somewhat similar results and this electrocardiographic pattern has been accepted as evidence of myocardial anoxia.

The "two-step" test of exercise tolerance, introduced by Master and E. T. Oppenheimer in 1929,²⁰ employs a standardized amount of exercise and is based upon the pulse and blood pressure response of normal subjects. More recently, Master

has combined this with electrocardiographic studies as a test of cardiac function and coronary insufficiency^{18,19} and has stressed the importance of standardized exercise. The criteria adopted for a positive test include a depression of the *RS-T* segment of more than 0.5 mm. in any lead or the conversion of an upright *T* wave to an isoelectric or inverted *T*, or the reverse. In one study,¹⁸ 83 patients with anginal syndrome were tested and positive results were noted in 30 to 46%, depending upon whether the "standard" or "double standard" test was employed. Favorable results have also been reported by Twiss and Sokolow,³⁵ Levay,¹³ and Feil and Pritchard,⁸ who used a modification of the Master "Two-Step" test.

On the other hand, Riseman, Waller and Brown,²⁷ studying a small group of subjects, concluded that the effects of exercise on the electrocardiogram of patients with anginal syndrome and of normal controls were "not sufficiently different to be of diagnostic value." A similar conclusion was reached by Sigler,³¹ who, however, did not mention the form or amount of exercise employed. Master has maintained that the criteria of Riseman and his associates were not correct and that the only *RS-T* change of any significance is a depression below the isoelectric level.

Variations in the rate and total amount of exercise as well as in the electrocardiographic criteria adopted for a positive result may account, in part, for the divergence of opinion concerning the value of the test. Further study of the electro-

cardiographic response to exercise as a test for coronary insufficiency seemed indicated.

Selection of Material. A total of 163 subjects was studied. They fall into the following groups: (1) 37 normal individuals who served as controls; (2) 91 patients with heart disease; (3) 13 additional subjects originally in the control group but subsequently eliminated because they failed to fulfill all the criteria for this group; and (4) 22 patients convalescing from recent acute illness.

could be excluded. There were 22 males and 15 females, with an age distribution of 20 to 62 years.

In all patients with heart disease, diagnostic classification (Table 2) was established in accordance with the criteria of the New York Heart Association.²³ There were 66 males and 25 females, with an age distribution of 29 to 75 years (Table 1).

Of the 13 subjects eliminated from the normal control group, 9 presented some abnormality of the control electrocardiogram. Other findings included hypertension, evidence of cardiac enlargement and, in 1

TABLE 1.—AGE AND SEX DISTRIBUTION OF NORMAL CONTROLS AND PATIENTS WITH HEART DISEASE

Age	Normal controls		Patients with heart disease	
	Male	Female	Male	Female
20-30	12	0	0	2
31-40	3	7	5	1
41-50	3	6	12	1
51-60	2	2	28	14
61-70	2	0	14	5
71-80	0	0	7	2
Total	22	15	66	25

TABLE 2.—CLASSIFICATION OF CARDIAC PATIENTS ACCORDING TO ETIOLOGIC DIAGNOSIS

Etio logic diagnosis	No. of patients	Patients with positive test
1. Arteriosclerotic:		
(a) Coronary sclerosis	24	9
(b) Coronary sclerosis and previous myocardial infarction	15	4
Total	39	13
2. Arteriosclerotic and hypertensive	19	11
3. Arteriosclerotic and syphilitic	1	0
4. Hypertensive	12	3
5. Hypertensive and syphilitic	3	2
6. Rheumatic	3	1
7. Unknown (rheumatic type)	2	0
8. Possible heart disease	8	0
9. Possible and potential	2	0
10. Syphilitic	1	0
11. Pericarditis (complicating pneumonia)	1	1
Total	91	31

The members of the normal control group were selected on the basis of a negative history with respect to heart disease, normal physical signs and blood pressure, a normal electrocardiogram at rest and normal cardiac size and pulsations as determined by roentgenologic and fluoroscopic study. In 3 subjects an inverted *P* wave in Lead III was noted as an isolated finding and these were not eliminated. This group included medical students as well as hospital and clinic patients. The latter were selected only when such complicating factors as systemic disease, severe anemia and recent infection

instance, a history suggestive of heart disease.

The group tested during convalescence from acute illness included 13 males and 9 females with an age distribution of 18 to 58. The conditions from which these patients were convalescing were as follows: Bacterial pneumonia (10), primary atypical pneumonia (7), bacterial pneumonia with delayed resolution (1), "la grippe" (2), acute pharyngitis (1), and acute gastro-enteritis (1).

Method of Study. The "two-step" exercise test was performed according to the method of Master and his associates.^{18,19,20}

All electrocardiograms were recorded in the sitting position with an angle of 90 degrees between the backrest and seat of the chair. The subject rested for a minimum of 15 minutes. An attempt was made to perform each test at least 1 hour after the last meal and 1 hour after smoking. In a few instances, the latter condition was not fulfilled. The temperature of the room was not controlled. A two-step staircase was used with an elevation of 9 inches per step or a total elevation of $1\frac{1}{2}$ feet. A control electrocardiogram was taken with Leads I, II, III, and CF_4 recorded in that order. Blood pressure and pulse readings were taken repeatedly until stabilized within 2 points. With the electrodes in place, the subject then performed the required number of trips* across the staircase in exactly $1\frac{1}{2}$ minutes ("standard" test). The "double standard" test, when performed, consisted of twice the standard number of trips completed in 3 instead of $1\frac{1}{2}$ minutes. Upon completion of exercise, the subject sat down promptly and the 4 lead electrocardiogram was recorded. The average time required for this tracing was 75 seconds. Single blood pressure and pulse readings were taken 2 minutes after the completion of exercise and additional electrocardiograms were recorded at 4 and 10 minute intervals. All candidates were carefully questioned concerning symptoms experienced during or following exercise.

The Cambridge string electrocardiograph was employed throughout the study, both the stationary (Williams-Hindle) and mobile models being employed. All electrocardiograms were interpreted in accordance with the criteria of the New York Heart Association.²³ Leads I, II, and III were standardized so that 1 millivolt produced a deflection of 1 cm. and the precordial lead was standardized at one-half this sensitivity. Slight differences of standardization were taken into account in the comparison of the amplitude of deflections before and after exercise. Changes in the level of the *RS-T* junction were judged in relation to the level of the *P-R* interval. Estimates of the *RS-T* level were made only when the *T-P* interval of 2 and preferably 3 successive complexes followed the same horizontal line. This was found necessary since even slight wandering of the tracing produced an apparent change in the level of the *RS-T* junction.

The electrocardiographic criteria which

were adopted for a positive test are described below.

Results. 1. NORMAL CONTROL GROUP. Thirty-one subjects performed the "standard" and 6 performed the "double standard" test. In 6 members of this group there were no appreciable electrocardiographic changes following exercise. The changes noted in the remaining subjects are listed in Table 3 and are considered a normal response to exercise. Slight variations in the amplitude of the *R* and *T* waves were observed most frequently. These consisted of either an increase or decrease in amplitude, the latter being noted more often. The decrease in amplitude of the *R* waves ranged from 2 to 4 mm. and the *T* wave amplitude was never diminished by more than 1 to 2 mm. Marked changes in amplitude as well as direction of *T*₃ were noted in 4 instances.

In 1 subject, a 22 year old male who performed the "double standard" test, a depression of the *RS-T*₂ junction of 1 mm. below the *P-R* level was noted. This appeared only immediately after exercise during tachycardia and disappeared in the 4 and 10 minute tracings. This depression exceeds the maximum of 0.5 mm. allowed for normals under these test conditions.²⁵ Alterations in the level of the *RS-T* junction of Leads III and CF_4 were not observed. It should be noted that tachycardia had largely subsided in most instances during the recording of these leads.

The ingestion of food has been shown to produce a 30 to 50% decrease in the amplitude of *T* waves in some normal individuals.¹⁰ The possible effect of food on the electrocardiographic response to exercise was investigated. Five normal young men of the control group were subjected to the "double standard" test in the fasting state. Approximately 1 week later the tests were repeated 1 to $1\frac{3}{4}$ hours following a meal. The electrocardiographic response to exercise was similar to that noted during the fasting state. In 2 of the 5 subjects a slight decrease in the amplitude of *T*₁ and *T*₂ was noted in the electrocardiogram at rest following the ingestion of food as

* See tables of Master.¹³

TABLE 3.—ELECTROCARDIOGRAPHIC CHANGES FOLLOWING EXERCISE IN NORMAL CONTROLS

Electrocardiographic changes	No. of instances noted
P_3 from upright to diphasic	1
P_3 from inverted to upright	2
P_3 from inverted to isoelectric	1
Q wave changes	0
R_1 amplitude diminished	10
R_2 amplitude diminished	1
R_3 amplitude increased	1
R_4 amplitude diminished	1
$RS-T_1$ depressed 1 mm.	1
$RS-T_2$ depressed 0.5 mm.	4
$RS-T_2$ from elevation of 0.5 mm. to isoelectric	1
T_1 amplitude diminished	15
amplitude increased	3
T_2 amplitude diminished	4
amplitude increased	1
T_3 amplitude increased	4
from upright to inverted	1
from inverted to upright	1
from diphasic to upright	1
from inverted to diphasic	1
T_4 amplitude increased	1

TABLE 4.—DISTRIBUTION OF SIGNIFICANT ELECTROCARDIOGRAPHIC CHANGES IN CARDIAC PATIENTS WITH A POSITIVE TEST

Lead	Instances noted		
	I	II	CF ₄
R wave	1*
$RS-T$ depression	7	7	2
T wave changes	6	10	7
Total	13	17	10

* From normal to double intrinsicoid deflection.

compared with the corresponding tracing taken during the fasting state. The ingestion of food by normal individuals would thus appear to have little influence upon the electrocardiographic response to this degree of exercise, provided the test is performed 1 hour or more following the meal. On the other hand, Master has observed electrocardiographic changes if the test is performed less than 1 hour after the ingestion of food.¹⁷

On the basis of the findings in the control group, the following electrocardiographic criteria were adopted for a positive test: (1) A depression of the $RS-T$ junction of more than 1 mm. in Leads I, II, III or more than 0.75 in CF₄. A depression of, but not exceeding 1 mm. in the standard leads was regarded as significant only if it persisted beyond the brief period of tachycardia immediately following exer-

cise. (2) The conversion of an upright T wave to an isoelectric or inverted T in Leads I, II or CF₄. The reverse process as well as the conversion of an initially diphasic to an upright T was also considered significant in these leads. (3) Disturbances in rhythm such as the appearance of premature systoles or runs of coupling were also regarded as an abnormal response to the test.

2. PATIENTS WITH HEART DISEASE. The electrocardiographic changes following exercise were considered significant in 31 of 91 patients with heart disease (34.1%). The distribution of these electrocardiographic alterations according to leads appears in Table 4. If we consider only those patients in whom a definite diagnosis of coronary artery disease had been established (first 3 groups of Table 2), the test was positive in 24 of a total of

59 patients (40.7%). Since many of the reports in the literature are concerned only with patients with a history of anginal syndrome, it is important to subdivide subjects according to symptoms for purposes of comparison. In the present group, there were 31 patients with a history of typical anginal syndrome, 21 with questionable symptoms, and 39 patients who had never experienced pain. The results

the control electrocardiogram. Although the proportion of positive tests was greater in the group of patients with initial electrocardiographic abnormalities (55 as compared with 36%), this difference is not significant. In Table 5c, all patients with heart disease, irrespective of symptoms, are subdivided according to the control electrocardiogram and no significant difference in results is noted. In brief, al-

TABLE 5
(a) Classification of Cardiac Patients According to Symptoms of Anginal Syndrome

	No. of patients	Patients with positive test	% positive
Typical anginal syndrome	31	15	48 3
Questionable or atypical symptoms	21	5	23 8
No angina	39	11	28 2
	<hr/>	<hr/>	<hr/>
Total	91	31	34 1

(b) Further Subdivision of Patients With Typical Anginal Syndrome According to Control Electrocardiogram

	No. of patients	Patients with positive test	% positive
Control electrocardiogram normal	11	4	36 4
Abnormalities of ST and/or T wave in control electrocardiogram	20	11	55 0
	<hr/>	<hr/>	<hr/>
Total	31	15	48 3

(c) Classification of All Cardiac Patients According to Control Electrocardiogram

	No. of patients	Patients with positive test	% positive
Control electrocardiogram normal	24	6	25 0
Abnormalities of ST and/or T wave in control electrocardiogram	67	25	37 3
	<hr/>	<hr/>	<hr/>
Total	91	31	34 1

of the test in these subgroups are indicated in Table 5a. The proportion of positive tests was slightly greater in the group with anginal syndrome (48.3%) than in those with questionable symptoms or complete absence of pain (23.8% and 28.2% respectively). Recognizing the fact that the number of patients involved is relatively small, analysis indicates that this difference is probably not significant.* In Table 5b, the patients with angina pectoris are subdivided according to the nature of

though the number of patients is relatively small, it would appear that there is no significant correlation under present test conditions between the gross electrocardiographic response to exercise and a history of anginal syndrome or the presence or absence of ST and T wave abnormalities in the control electrocardiogram. A higher incidence of positive results among the subjects with anginal syndrome might have occurred had more patients experienced pain under test conditions.

* The standard error of difference was determined by the formuln $\sqrt{\frac{p \times q}{n_1} + \frac{p \times q}{n_2}}$. Comparing the electrocardiographic results in patients with and without angina pectoris (Table 5a), we have a standard error of $\sqrt{\frac{48.3 \times 51.7}{31} + \frac{28.2 \times 71.8}{39}} = 11.5$. The actual difference is 20.1% which is less than twice its standard error (2 x 11.5 or 23). The same method was used in the comparison of differences between the other groups noted in Table 5. (Hill, A. B.: Principles of Medical Statistics, 1937, Lancet Ltd., London.)

Only 10 of the 31 patients with a history of anginal syndrome experienced pain during the test. One reason for this is the fact that the total amount of work performed in each instance was predetermined and not necessarily continued until angina appeared. No attempt was made to lower the temperature of the room, a factor which may facilitate the appearance of pain.²⁷ Seven of the 10 patients who experienced angina showed significant electrocardiographic changes. There was no strict correlation between the persistence of pain and the electrocardiographic response, since 2 of the 3 patients with a negative test experienced angina throughout the recording of the electrocardiogram following exercise.

No serious reactions to exercise were observed in any of the patients tested. Mild dyspnea, fatigue, or pain were the only symptoms noted and these subsided within a few minutes of the completion of exercise.

The single precordial lead, CF₄, was of assistance in the detection of electrocardiographic changes in 10 patients. In 5 patients, or approximately one-sixth of those with a positive test, these changes were confined to the precordial lead. That the latter may yield positive information following exercise when the standard leads are negative has been noted by Missal²² and Puddu.²⁶ The value of the chest lead has been emphasized by Feil,⁷ and Twiss and Sokolow³⁵ reported that its use increased the number of positive tests by approximately 20%.

An increase in the total work performed within the limits of this test did not appear to influence the electrocardiographic results significantly. Fifty-five patients with heart disease performed the "standard" test, while 36 were subjected to the "double standard." Of those performing the "standard" test, 23 patients (42%)

were positive. Eight of the 36 patients performing the "double standard" (22%) had a positive test. In addition, 20 patients who presented no significant electrocardiographic changes following the "standard" amount of exercise were later subjected to the "double standard" test. Only 3 of these developed a positive test with this increase in the total work performed.

A failure of the pulse or blood pressure to return to within 10 points of the resting level within 2 minutes after exercise is regarded as an abnormal response²⁰. Fifty-four of the 91 patients with heart disease showed a lag in the return of pulse, blood pressure or both. A lag in the return of blood pressure, usually systolic, to resting levels was noted most frequently, occurring in 37 patients. There was no significant correlation between a positive electrocardiographic test and diminished exercise tolerance (lag of pulse or blood pressure).† It should also be noted that, among the 37 normal controls, there were 7 with a delay in the return of pulse, blood pressure, or both.

3. SUBJECTS ELIMINATED FROM THE CONTROL GROUP. Of the 13 individuals falling into this category, 4 showed electrocardiographic changes following exercise not noted in the normal control group. The changes which are considered of possible significance include the appearance of auricular or ventricular premature systoles and, in 1 instance, the conversion of an initially diphasic to a low upright T wave in CF₄. The possibility of heart disease existed in all 4 patients, although a definite diagnosis was not made. None of these patients presented symptoms of heart disease and all had been hospitalized for complaints unrelated to the cardiovascular system.

4. PATIENTS CONVALESCING FROM ACUTE ILLNESS. The exercise test was

† Of 31 patients with a positive electrocardiographic test, 21 had diminished exercise tolerance (67.7%). Of 60 patients with a negative electrocardiographic response, 33 had diminished exercise tolerance (55%). The standard error of this difference = $\sqrt{\frac{67.7 \times 32}{31} + \frac{55 \times 45}{60}} = 10.6$

The actual difference (12.7%) is much less than twice its standard error ($2 \times 10.6 = 21.2$).

performed after the patients had been ambulatory for 1 to 7 days and had been afebrile for 2 to 21 days. In general, the electrocardiographic changes noted were similar to those of the normal control group. Four patients convalescing from pneumonia showed a depression of the *RS-T* junction of 1 mm. following exercise. Inasmuch as a similar change had been noted in but a single member of the normal control group, further observations of these patients seemed indicated. In 1 patient antecedent heart disease could not be excluded because of evidence of slight cardiac enlargement on teleoroentgenogram. The remaining 3 patients presented no evidence of heart disease. All showed a depression of the *RS-T₂* junction of 1 mm. immediately after exercise. It was possible to follow 2 of these subjects over a period of several weeks while the third was not available for further study. In the 2 patients who were followed, the *RS-T* depression following exercise diminished to a fraction of a millimeter after the second week out of bed and remained at that level. Since the standard amount of exercise had produced a more marked tachycardia during early convalescence, the possibility arose that tachycardia alone might be responsible for the change noted. For this reason, after the standard test showed only minimal changes, the same degree of tachycardia noted during early convalescence was induced by the working of a foot pedal against resistance. Under the latter conditions, the *RS-T* junction was not depressed by more than a fraction of a millimeter. It was concluded that some factor other than tachycardia had been responsible for the depression of *RS-T* following exercise during early convalescence. At the time of the first test the chest film showed complete resolution of the pneumonic process in 1 patient and only a small area of consolidation in the other. It is of interest to note that Master¹⁹ describes a "positive" test in a 20 year old male with an unsuspected virus pneumonia followed by a negative test after complete recovery from the infection.

Discussion. The effect of exercise on the electrocardiogram is governed by a number of variables which must be considered in the interpretation of results. In a patient with diminished coronary reserve due to coronary artery disease it is possible to produce or intensify an alteration in the physicochemical state of the myocardium by increasing the work of the heart. A disproportion between the requirements of the myocardium and the coronary blood flow is created or intensified. Areas of ischemia or ischemia plus injury presumably develop for a variable period of time and modify the normal processes of accretion and regression in and about the areas involved. An area of injury would cause displacement of the *ST* segment³⁸ and areas of ischemia would be associated with *T* wave changes.² However, the complexity of the conditions involved are such as to make prediction of results somewhat difficult. The size and distribution of the areas of ischemia and injury and, more specifically, their spatial relationship to the standard and precordial leads will influence the results. The degree or intensity of these processes as well as their location and extent must also be considered. Both in theory as well as in fact, it is possible for an area of ischemia or injury to be so situated as to exert little or no effect upon the standard or precordial leads. Moreover, if the process is diffuse, it is conceivable that the abnormal electrical effects exerted in one direction as a result of an alteration in the physical state of the myocardium may be completely nullified in the recorded electrocardiogram by similar effects operating in a diametrically opposite direction. These considerations may account at least in part for the occurrence of a substantial number of negative tests in patients with known coronary disease and diminished coronary reserve. They may also account to some extent for the failure of a certain proportion of patients to manifest electrocardiographic changes during paroxysms of angina pectoris, whether spontaneous or induced. Another possible explanation is the pro-

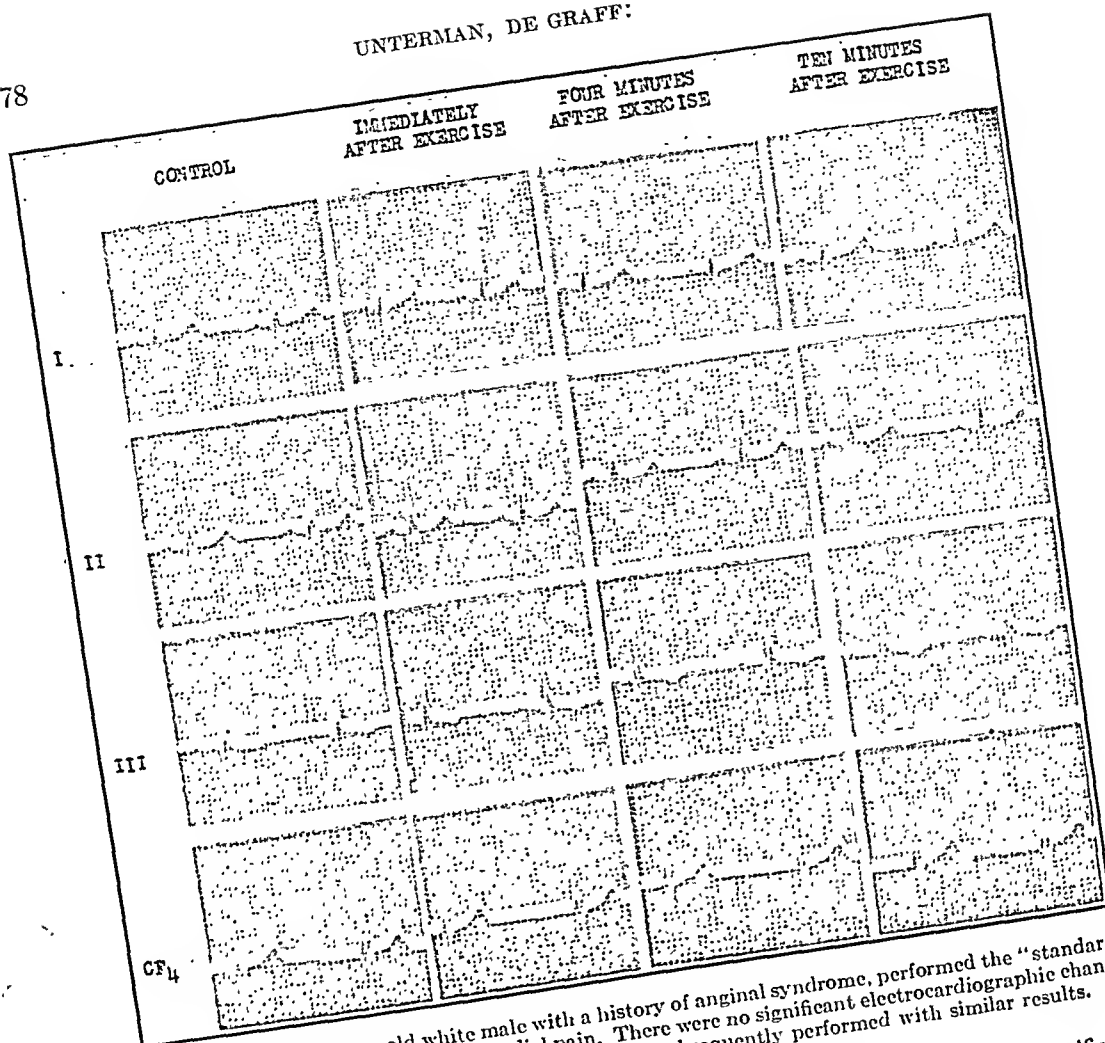


FIG. 1.—G. M., 55-year-old white male with a history of anginal syndrome, performed the "standard" test during which he experienced precordial pain. There were no significant electrocardiographic changes following exercise. The "double standard" test was subsequently performed with similar results.

duction of pain in certain cases by some mechanism other than that of myocardial ischemia. Other variables in the test include such technical features as the time relationship between the actual recording of the individual leads and the appearance and disappearance of areas of ischemia or injury which may influence these leads by virtue of their three dimensional position in space.

Case Reports. CASE 1. The patient, G. M., was a 55 year old male with a diagnosis of coronary sclerosis and a typical history of anginal syndrome. There was evidence of mild cardiac failure and the patient was on maintenance doses of digitalis leaf. The control electrocardiogram showed normal sinus rhythm and no deviation of the

electrical axis. There were no significant changes following the "standard" and "double standard" tests although the patient experienced anginal syndrome on both occasions (Fig. 1). It is believed that this patient's coronary reserve was sufficiently taxed under test conditions as evidenced by the appearance of precordial pain. It is obviously impossible to theorize as to which areas of the myocardium were subjected to increased ischemia or injury during the test. The failure of significant electrocardiographic changes to occur may be explained, at least in part, by the theoretical considerations mentioned above.

CASE 2. This case, by contrast, affords an example of a positive test which may be explained or even anticipated on theoretical grounds, since the probable distribution of

damaged myocardium was known. The patient, E. B., was a 36 year old colored male who had recovered from a virus pneumonia complicated by pericarditis with effusion. There was no evidence of antecedent heart disease. During the course of his illness, serial electrocardiograms showed *ST* segment and *T* wave changes compatible with pericarditis (Fig. 2). The exercise test was performed on the 43rd hospital day after all evidence of pneumonia and pericardial effusion had disappeared and the patient had been ambulatory for 1 week. The control electrocardiogram showed upright *T* waves in Leads I and II and an inversion of *T*₄. Following exercise there was definite inversion of *T*₂ and restitution was not yet complete in the 10 minute tracing (Fig. 3).

time of the test, the effects of exercise may be explained. With the more or less uniform development or intensification of ischemia over this distribution of myocardium as a result of exercise, the mean direction of the normal process of repolarization would be altered or reversed. The subepicardial location of the ischemic zone in the form of a half shell, open at the base and closed at the apex of the heart, would tend to reverse the mean direction of the forces of repolarization. The resultant force, projected as a vector upon the frontal plane, would be expected to alter the *T* waves of Leads I and II. The actual results in this case fulfill the anticipated results in part.

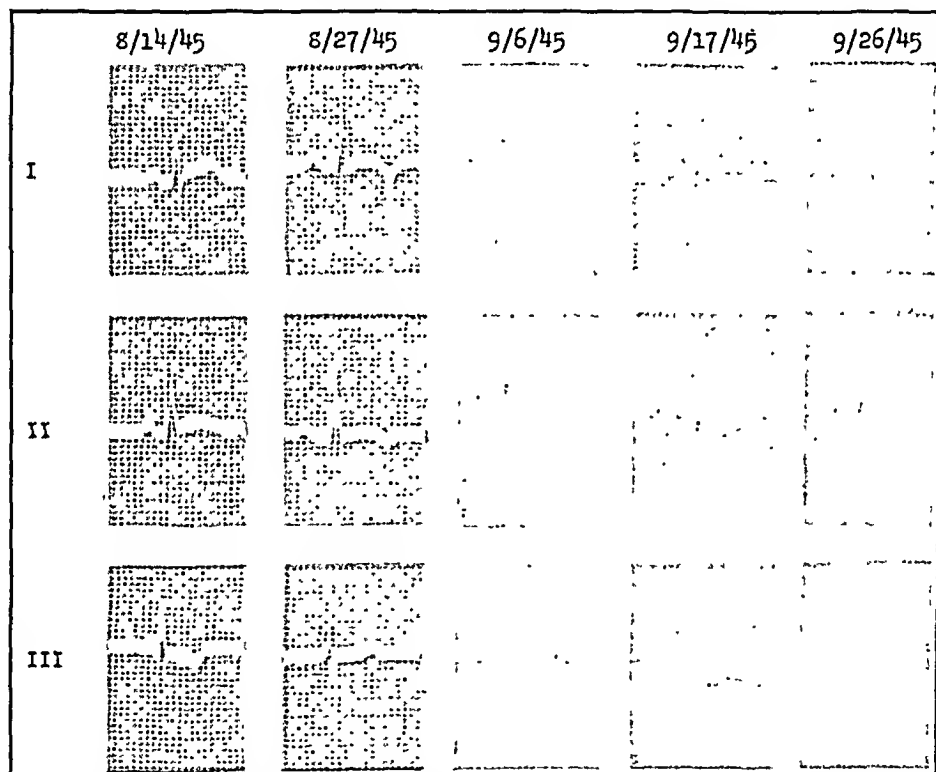


FIG. 2.—Serial electrocardiograms taken during the course of a virus pneumonia complicated by pericarditis with effusion in a 36-year-old colored male. There was elevation of the *ST* segments of Leads I and II followed by return to the isoelectric level with inversion of *T*₁ and *T*₂. Subsequent tracings showed return of *T*₁ and *T*₂ to the upright position.

The primary *T* wave changes which occur in diffuse pericarditis have been explained by the assumption that the damaged subepicardial zone of the myocardium behaves as though it were ischemic.² If some degree of subepicardial damage still existed in this patient at the

The occurrence of a negative result in at least one-half of all patients with known coronary insufficiency detracts somewhat from the practical value of the test. In several problem cases which were studied, the diagnosis depended entirely upon a questionable or atypical history of anginal

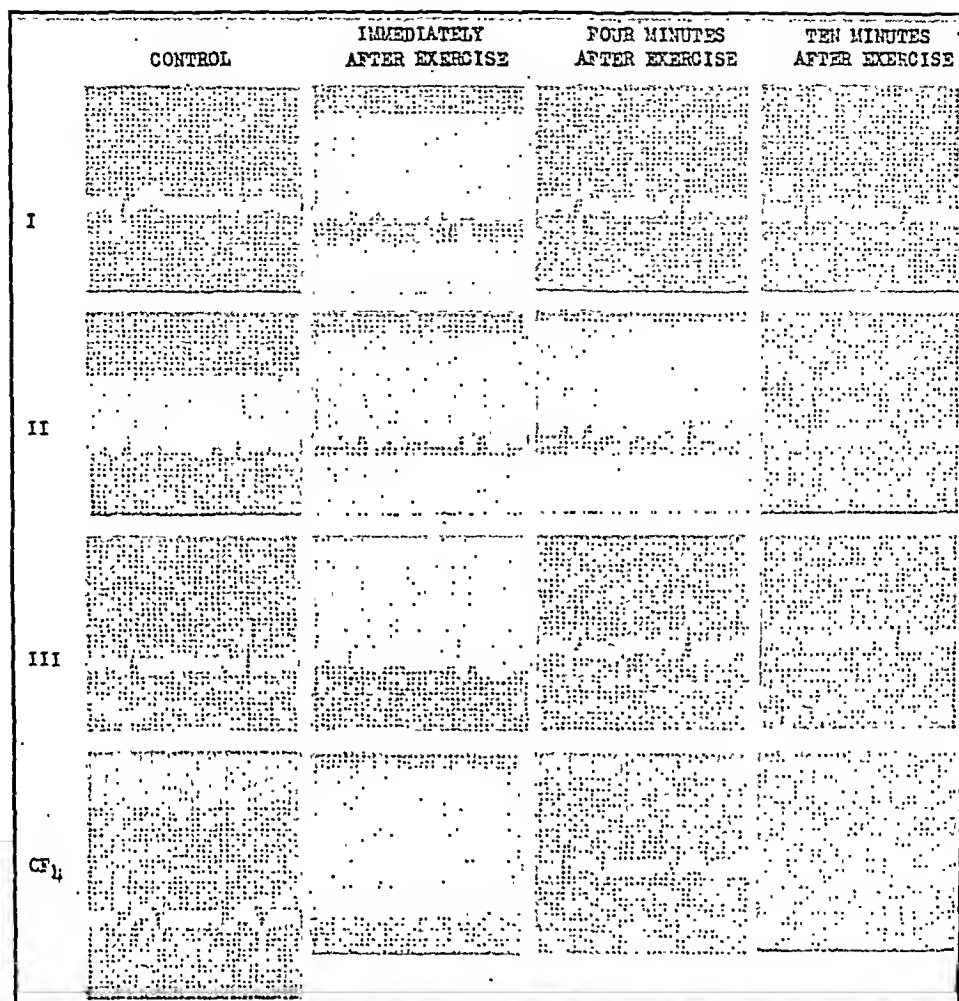


FIG. 3.—E. B., the same patient whose electrocardiograms appear in Figure 2, performed the "standard" test following recovery from a virus pneumonia complicated by pericarditis with effusion. The *T* wave of Lead II became sharply inverted in the electrocardiogram recorded 4 minutes after exercise and restitution was not complete in the 10 minute tracing.

syndrome, all other findings being normal. In all of these, the exercise test was negative and a diagnosis of coronary insufficiency could neither be established nor excluded. In such cases the final diagnosis must depend upon further evaluation of symptoms and the subsequent clinical course. These factors remain the most important guides in the diagnosis of coronary insufficiency.

In view of the possible criticism that our electrocardiographic criteria were too severe, the results listed in Tables 2 and 5b were recalculated, using an *RS-T* de-

pression of more than 0.5 instead of 1 mm. as indicative of a positive test. The material studied was exactly the same except that one additional patient with typical anginal syndrome had been added to the group. The results were now positive in 41 of 92 patients with all types of heart disease (44.6%) and in 31 of 60 patients with known coronary disease (51.7%). In the group of 32 patients with typical anginal syndrome, the results were now positive in 20 (62.5%). This still leaves a relatively large proportion of the patients with known coronary insuffi-

ciency with a negative test. Moreover, the appearance of an electrocardiographic change of similar magnitude (*RS-T* depression of more than 0.5 mm.) in one of the controls who was normal in every respect makes it difficult to accept such a change as distinctly abnormal. Biorck has also expressed the view that an *RS-T* deviation of only 0.5 mm. as the upper limit of normal is too liberal in the interpretation of results.³

Emphasis has been placed on the necessity for the rapid recording of all 4 leads immediately following exercise in order to detect significant changes which may rapidly disappear.¹⁹ For this reason, the Cambridge "Simpli-Trol" was employed in the study of 11 patients with typical anginal syndrome. The electrocardiogram immediately after exercise was recorded in a maximum of 30 to 40 seconds. Ten patients had previously yielded negative results with the slower technique requiring 75 seconds to record the electrocardiogram and 1 patient had not been studied before. Only 2 of the 11 patients showed significant electrocardiographic changes with the rapid recording technique. Recalculation of the results using an *RS-T* depression of more than 0.5 mm. for a positive test, gave a positive result in only 4 of the 11 patients studied.

In spite of these limitations, it should be noted that the test was occasionally of aid in providing objective evidence of coronary insufficiency. The following cases are briefly presented as examples of this type:

CASE 3. R. M., a 39 year old white male, complained of substernal pressing pain brought on by exertion and relieved by rest. Physical and roentgenologic examination as well as the control electrocardiogram were negative. The standard exercise test gave equivocal results but the "double standard" test was positive, showing significant depression of the *RS-T* junction of Lead II (Fig. 4). The patient experienced substernal and left shoulder pain during the test. The "double standard" test was repeated 2 months later following a 2 week course of theobromine with sodium salicylate (0.5 gm. q.i.d.) with similar results (Fig. 4).

CASE 4. S. S., a 57 year old white male, complained of pressing precordial pain appearing on exertion and relieved by rest and nitroglycerine. Electrocardiograms at rest were normal except for 1 tracing recorded during a spontaneous paroxysm of pain, which showed *ST* segment depression in the standard leads and *ST* depression and *T* wave inversion in Lead V_3 . The standard exercise test was performed and the patient completed only 15 out of 18 trips because of the onset of precordial pain. Following exercise there was a significant depression of the *RS-T* junction in Leads I and II and a conversion of T_2 from upright to diphasic (Fig. 5). In this case, objective evidence of coronary insufficiency had been obtained in the tracing recorded during a spontaneous paroxysm of pain so that the exercise test merely provided confirmation. This case is presented, however, because of the interesting similarity between the changes observed during the spontaneous and induced episodes of pain.³⁹ The alterations noted during the spontaneous attack were more striking.

The effect of digitalis on the normal work electrocardiogram has been studied by Zwillinger⁴⁰ and by Liebow and Feil.¹⁶ The latter found that, following digitalization, significant *ST* segment and *T* wave changes occurred in some normal individuals after the performance of 100 trips across the two-step staircase. Since this represents approximately 2 to 5 times the total amount of work performed by our subjects, the effect of digitalis was studied again under present test conditions. A normal 43 year old male performed the "double standard" test (46 trips in 3 minutes) with no significant electrocardiographic changes. He was then digitalized and the test was repeated. The control electrocardiogram now showed *ST* segment depression and diphasic *T* waves in Leads II and III but no change in Lead I. Following exercise, however, T_1 was converted from upright to diphasic and ST_1 was depressed. This indicates that digitalis may influence the electrocardiographic response to exercise under present test conditions. Nineteen of the patients with heart disease were on maintenance doses

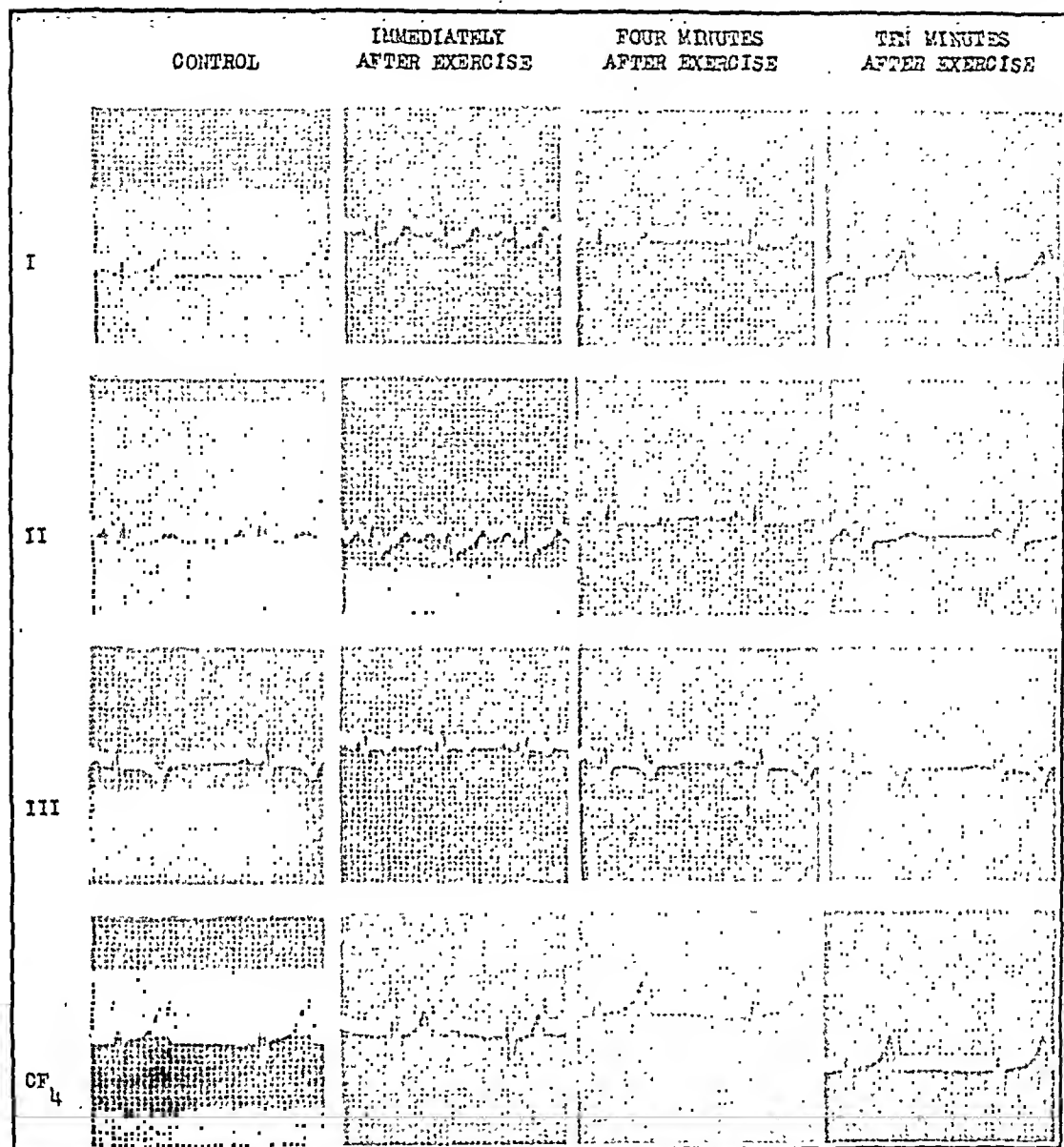


FIG. 5—S. S., a 57-year-old white male, completed only 15 out of 18 trips because of the onset of precordial pain. There was a significant depression of the *R-ST* segments of Leads I and II immediately after exercise and conversion of *T*₂ from upright to diphasic in the 4 minute tracing.

of digitalis at the time of the test and in 6 of these the results were positive (32%). Of the 72 patients who were not receiving digitalis, 25 (35%) were positive. Since these patients were not studied both before and after digitalization, it cannot be stated whether digitalis played a significant rôle in the determination of results. In view of the findings in normal individuals, however, the possible influence of the drug should always be considered.

The electrocardiographic response to exercise in patients convalescing from

acute infections is of interest. Although only 4 of the patients tested showed more than a minimal alteration, the subsequent disappearance of these changes in the 2 subjects who were followed is of possible significance. Electrocardiographic abnormalities during the course of pneumonia have been described^{1,6,21,24,29,32,33} and have included disturbances of rhythm and conduction as well as changes in the auricular and ventricular complexes. Slight elevation or depression of the *RS-T* junction has been noted in a small number of

patients.^{14,21,24,29,33} Some of the changes have been observed during the postfebrile period and have been interpreted as possible evidence of active disease processes of the heart. The persistence of some alteration in the state of the myocardium during early convalescence, not manifest at rest but reflected in the electrocardiographic response to exercise, may explain the slight changes we have observed and their subsequent disappearance.

Summary and Conclusions. 1. The Master "two-step" exercise test was performed in 163 subjects including controls, patients with heart disease and patients convalescing from acute illness.

2. The electrocardiographic changes following exercise were regarded as significant in 40.7% of 59 patients with coronary disease and in 48.3% of 31 patients with

anginal syndrome. No serious untoward reactions to exercise were noted.

3. The electrocardiographic response was positive in 7 of 10 patients who experienced anginal syndrome during the test.

4. A small number of patients with a negative "standard" test showed a positive test when the "double standard" exercise was performed.

5. The test provides a means of determining coronary insufficiency when other means are not available, although it does not do so in all cases. The practical value of the test appears to be limited by a high incidence of negative responses.

6. The theoretical aspects of the test are discussed. The possible influence of different electrocardiographic techniques and criteria as well as the influence of food, digitalis and recent acute illness are considered.

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THE TREATMENT OF ANURIA BY INTESTINAL PERFUSION

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ANURIA with its concomitants of increasing azotemia and uremia is not uncommon. It may follow such widely diversified conditions as transfusions with incompatible blood or other hemolytic reactions, severe burns, prolonged shock, the crush syndrome, toxemia of pregnancy, certain operations—notably transurethral resection or simple retrograde urologic studies; also the administration of sulfonamides, certain of the heavy metal poisons, and a great group of other organic compounds related to carbon tetrachloride.

The mortality rate in such cases, unfortunately, is high because of the rapid accumulation of nitrogenous and other waste substances in the body which normally would be excreted by the kidneys. Often irreversible renal lesions cannot be demonstrated at postmortem examination. The problem in such instances, then, is to tide the patient over that period of renal insufficiency until such time as the damaged kidneys can resume their normal functions.

The concept of treating acute renal insufficiency by extrarenal excretion is not new. Abel, Rowntree and Turner,¹ in 1914, were the first to devise a method for external dialysis by means of an "artificial kidney." The skin has been utilized in the past as a route of excretion by means of baking, tubbing and diaphoresis. Nor is the use of the gastro-intestinal tract as a means of extrarenal excretion new. Purging, gastric lavage, repeated enemas have all been attempted. Recently Rogers, Sellers and Gornall² have shown that when surgically isolated loops

of bowel are perfused in nephrectomized dogs, the blood non-protein nitrogen can be reduced.

Peritoneal lavage, in vogue at the moment, was first employed by Gantner,³ in 1923; and was recently revived by Frank, Seligman and Fine.² Nonetheless, the use of the peritoneum has certain practical objections: (1) the need for strict aseptic technique and the potential infection of the peritoneum by organisms not susceptible to available antibiotics; (2) mechanical difficulties encountered in the elaboration of fibrin by the peritoneum and the reduction of its efficiency as a dialyzing membrane when covered with a plastic fibrinous exudate; and (3) the necessity of operating upon a patient already critically ill, to invoke its use.

The utilization of the small intestine as a dialyzing membrane with volume flow of perfusate comparable to that maintained in peritoneal lavage has never, to our knowledge, been attempted in humans. Yet the small intestine appears to be the ideal dialyzing membrane for the following reasons: (1) it is accessible without operation; (2) with its "corrugated" surface and great length it presents a large surface area; (3) notoriously, it imposes a barrier to infection; and (4) one of its most important functions under normal conditions is to permit diffusion in both directions.

The following case is reported in which massive intestinal perfusion was employed:

Case Report 1. A 45 year old woman was admitted to the hospital, Sept. 23, 1947, on the service of Dr. C. E. Schlichtman. A his-

tory was obtained from friends that she had been drinking alcohol excessively and that on the preceding day had ingested an indeterminate amount of cleaning fluid. This was subsequently determined to contain a number of ingredients, including naphthalene, glycol ether and a variety of hydrocarbons, ranging in volatility between gasoline and kerosene.

On examination she was found to be disoriented, confused and restless. The temperature was 39° C. and the pulse rate 120 per minute. A few fine crepitant râles were heard at the right lung base. The heart was normal and its rhythm regular. Blood pressure was 100/70. The lower margin of the liver was tender and extended 3 cm. below the right costal margin. The spleen was not felt. The extremities were normal and there was no edema. The blood contained 15.5 gm. of hemoglobin and the white blood cells numbered 21,000.

as shown in Figure 1, and all subsequent specimens contained large amounts of albumin, white blood cells, epithelial cells and granular casts.

By the 5th hospital day she was completely comatose and the blood non-protein nitrogen was 330 mg. per 100 cc. Intestinal perfusion was started through 2 Miller-Abbott tubes placed in the small intestine as shown in Figure 2. At the end of 12 hours, approximately 22 liters of fluid had run through and the blood non-protein nitrogen had dropped to 121 mg. Twelve hours later it was found to be 66 mg. The concentration of non-protein nitrogen in the initial sample of perfusate was 50 mg. per 100 cc. Intestinal perfusion was continued in this fashion for 7 days. Then, because of the increasing urine output, the perfusion operation was maintained only on a half time basis and then completely discontinued. At this time she looked well clinically, was

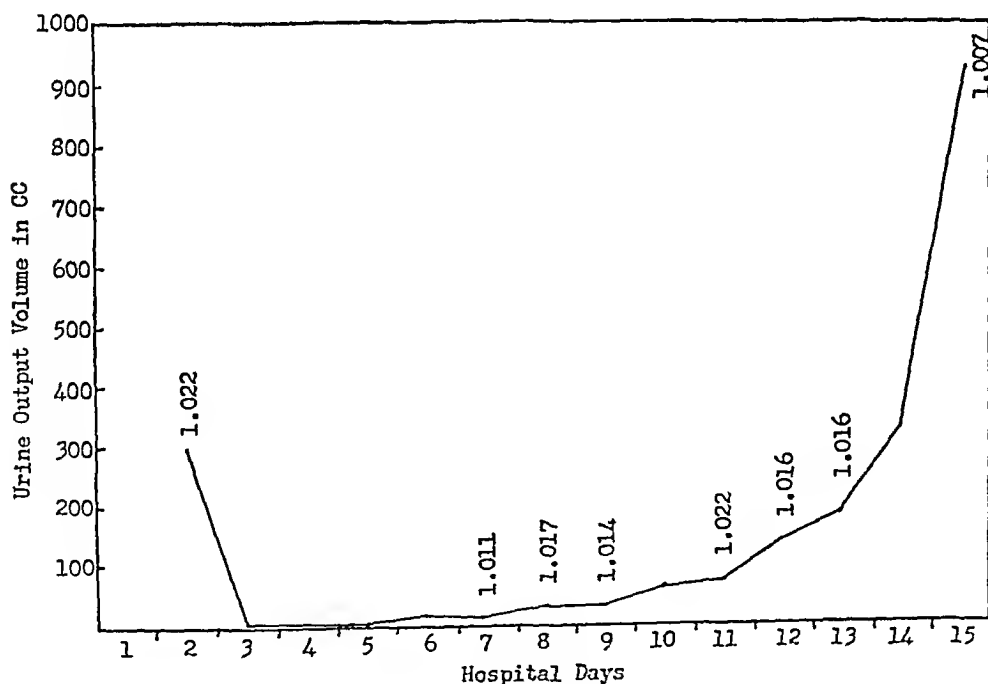


FIG. 1.—Graph of urine output.

The following day she was definitely jaundiced with the lower liver margin extending downward below the iliac crest. Icteric index was found to be 36. On this day 300 cc. of urine were obtained, containing no albumin, a normal sediment and a specific gravity of 1.022. This was evidently (partly at least) residual urine antedating the nephrotoxic action of the cleaning fluid. The urine output then dropped off abruptly,

oriented, rational and complained of no distress. The jaundice had disappeared and the liver edge receded to the costal margin. However, during the next 48 hours the non-protein nitrogen rose from 49 to 103 mg. and the creatinine from 11.2 to 12.3 mg. per 100 cc., whereupon treatment by perfusion was reinstituted.

In the preceding 4 days increasingly frequent extrasystoles had developed and there

was a noticeable decrease in the duration of systole. On the evening of the 15th hospital day (the 10th day of intestinal perfusion), while talking to the nurse, she gasped and suddenly expired. Studies of the blood taken within 24 hours before death revealed the following: total protein, 5.9 gm. per 100 cc., with the albumin fraction 3.3 gm.; calcium, 9.4 mg.; phosphorus, 4.1 mg.; sodium, 139.5 mEq./L. and serum potassium (not reported until after death), 1.1 meq./L.

NECROPSY. The *brain* was found to be normal except for mild edema. Each pleural cavity contained about 200 cc. of clear fluid. The *lungs* showed only moderate edema. The *heart* appeared to be normal both grossly and microscopically. The pericardial sac contained about 30 cc. of clear fluid. There was no evidence of a fibrinous pericarditis. The abdominal cavity contained about 1000 cc. of transudate. The *small intestine* showed slight edema of its coats but was not otherwise remarkable. In the retroperitoneal tissue, just distal to the ligament of Treitz, there was an ecchymosis about 3 by 4 cm. in extent. Otherwise no areas of hemorrhage were seen. The *liver* weighed 1590 gm. Its capsule was brownish and wrinkled. On section, accentuation of the central zone markings was noted, giving somewhat the appearance of a nutmeg liver. Microscopically, all of the lobules showed extensive central necrosis. The sinusoids at the periphery were normal. The *kidneys* were considerably enlarged, the right weighing 315 gm. and the left 310 gm. The external surfaces were smooth and pale. The capsules stripped easily. The cut surfaces were moist and edematous. The cortex was slightly thickened, the structural detail was somewhat hazy and the corticomedullary junctions were poorly defined. Microscopically, the glomeruli showed moderate congestion. There were occasional areas of lymphocytic infiltration in the interstitial tissue. The proximal and distal convoluted tubules showed marked cloudy swelling and were somewhat dilated. The lumina contained small amounts of amorphous material. Occasional tubules contained bile-stained casts.

Discussion. In the care of this patient 3 types of problems were involved: (1) general problems in medical management; (2) mechanical problems with regard to

placement, maintenance and operation of the tubes; and (3) chemical problems in the maintenance of water, electrolyte, and acid base balance.

At the onset, financial considerations precluded special nurses in constant attendance, certain laboratory procedures which would have been helpful in management, and the use of buffered electrolytically balanced hyperosmolar solutions. As the utter hopelessness of the situation was gradually abandoned, and the picture brightened, some of these advantages became available to us.

Attempt was made to maintain nutrition by intravenous administration of 1000 cc. of plasma daily. An indeterminate amount of glucose was also absorbed from the perfusion fluid. Additional parenteral vitamins would have been desirable, but these were never given.

As the patient roused from coma, she became restless and noisy, increasing the difficulty of nursing care. The use of sedatives was carefully considered, inasmuch as their excretion rate in an anuretic individual was an unknown factor. It was finally decided to administer paraldehyde parenterally, as its excretion is largely pulmonary. This proved to be an ideal sedative in doses of 5 to 8 cc. as often as required. No harmful effects from the drug were detected.

The Miller-Abbott tubes were passed orally in the usual manner. The first was placed in the duodenum and the balloon inflated before attempt was made to pass the second. All in all, the patient pulled out both tubes twice and vomited the proximal tube on 1 occasion. The former accident was prevented subsequently by more constant nursing care, hand restraints and the liberal use of paraldehyde. It was felt that vomiting was produced by reflux of fluid into the stomach, producing distention which initiated the vomiting reflex. This was never again encountered when the proximal tube was anchored in the third portion of the duodenum. The perfusing fluid was administered by drip method through the proxi-

mal tube with its balloon deflated. The rate of flow was always maintained as high as was mechanically possible. Initially, because we were uncertain as to the amount of trauma and edema which would be produced in the small intestine by this massive flow, relatively long "rest periods" were ordered. However, as we became more familiar with the method, and as the patient became conscious,

anchored at that point. The bag was then partially deflated. On the following day the distal end of the tube was seen to emerge from the rectum. Evidently the bowel had shortened and threaded itself over the tube. Following this, by means of the fluoroscope, the distal end of the tube was withdrawn to a position in the terminal ileum and the bag still further deflated with no subsequent trouble from

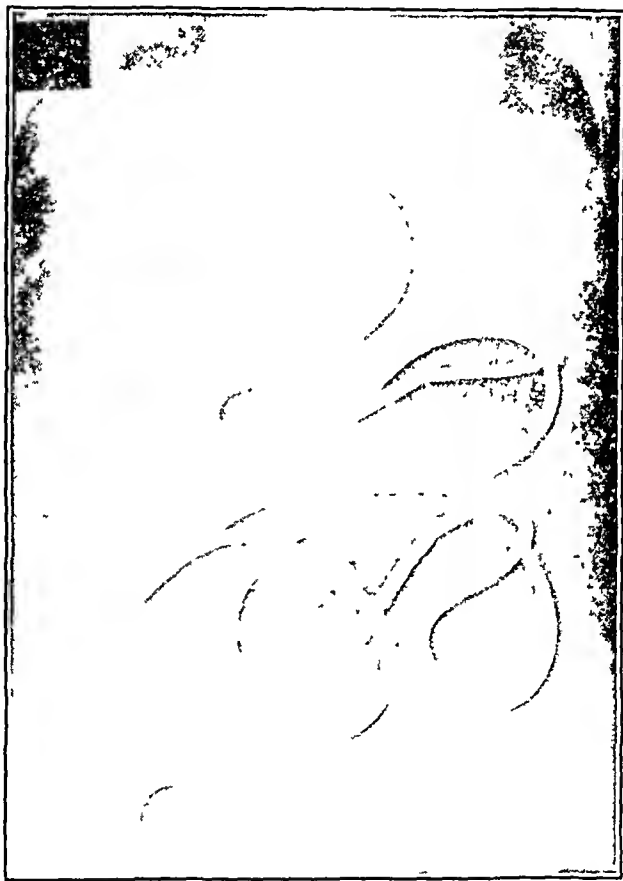


FIG. 2.—Roentgenogram of Miller-Abbott tubes in intestine.

more coöperative, and rarely complained of pain, these "rest periods" were gradually shortened empirically to 5 minutes out of every hour. It is questionable whether they were at all necessary. Ordinary Baxter suction was applied to the distal tube which was allowed to migrate to the ileum as shown in Figure 2. After reviewing this roentgenogram it was felt that a still greater perfusing area should be utilized and, accordingly, 3 more feet of tubing were inserted and the tube then

"migration." On several occasions a tube was inserted into the rectum and the distal bag completely deflated in order to bring the entire intestinal tract into use as a perfusing surface. This, however, was found to increase the difficulty of nursing care and make the measurement of output more inaccurate without appreciably increasing the effectiveness of the operation. Occasionally the distal tube became obstructed, following which the abdomen rapidly distended and the rate

of inflow automatically decreased. During these periods, complete deflation of the bag along with rinsing of the tube with air or saline was all that was necessary to reestablish normal function. It was apparent at the outset that if carefully balanced fluids such as modified Tyrode's solution as suggested for peritoneal lavage could have been utilized in this case, our problems in electrolyte, water and acid base balance would have

chloride, 1 gm. each, per liter of tap water which had been warmed to body temperature. In the first 24 hours, 42.7 liters of this solution were instilled. The fall of blood non-protein nitrogen from a level of 330 mg. just prior to the onset of treatment to 121 mg. in 12 hours and to 66 mg. at the end of 18 hours of treatment was most gratifying. However, by this time a positive fluid balance of over 6 liters had been achieved which was easily apparent in

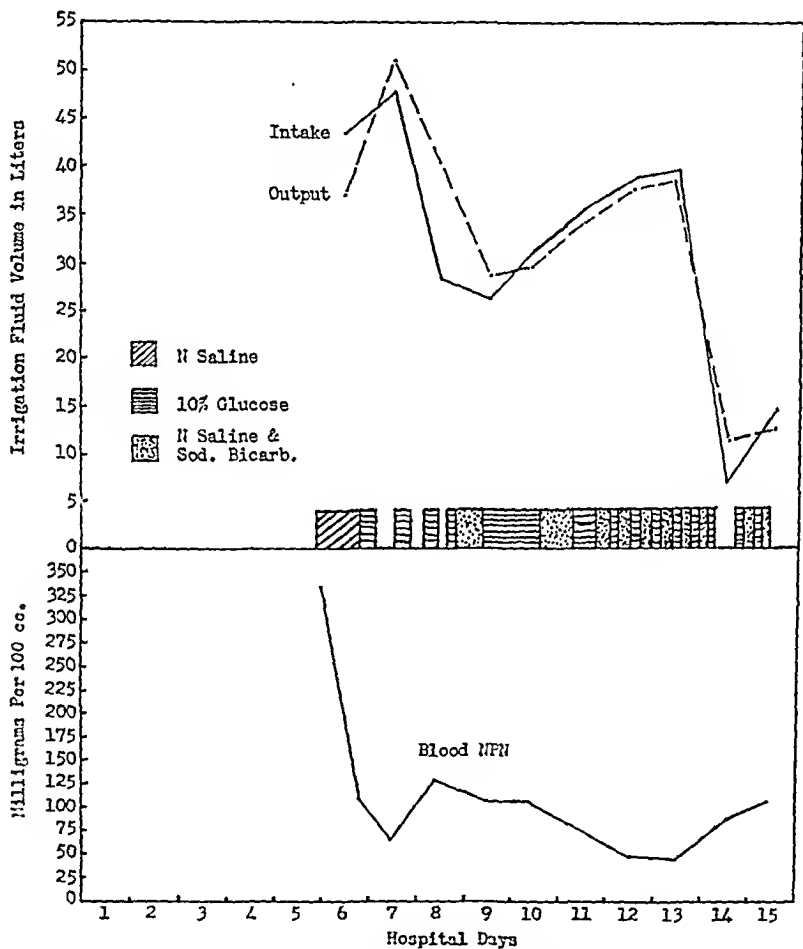


FIG. 3.—Intake and output volume of perfusion as compared to blood non-protein nitrogen.

become greatly minimized and indeed, probably would have permitted recovery. These solutions were not available to us at the time. Accordingly, perfusion was begun with saline prepared by the simple expedient of dissolving 9 tablets of sodium

the development of massive edema. Although the saline solution was roughly isotonic, increased intraluminal pressure and other factors undoubtedly aided in the absorption of sodium which allowed the development of edema. At this point

10% glucose was substituted for saline in the perfusion fluid with subsequent development of a negative water balance and corresponding decrease in edema. This eventually led to clinical acidosis with moderate hyperpnea. The blood sugar level was 270 mg. per 100 cc., no ketone bodies were found in the small amount of urine obtainable, and there was no reason to suspect ketosis. Determination of the plasma bicarbonate was not possible at the time.

carbonate was thereby converted to carbonic acid and blown off as carbon dioxide. At any rate, the perfusion fluid was again changed to include 8 gm. of sodium chloride and 1 gm. of sodium bicarbonate per liter. The patient was followed along in this manner with the perfusion fluid altered frequently to correct the clinical picture at the moment inasmuch as complete laboratory data were never available.

The level of the blood non-protein nitrogen was maintained roughly inversely

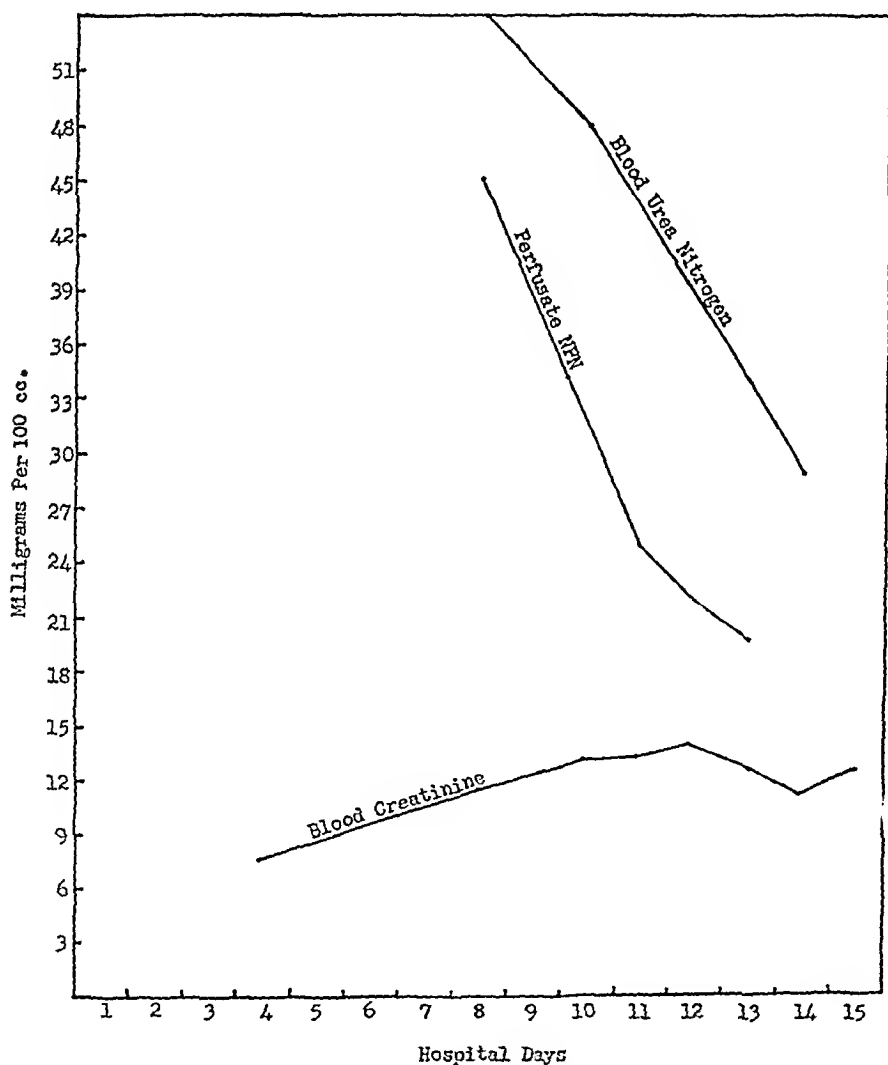


FIG. 4.—Comparisons of levels of blood urea nitrogen and blood creatinine with the non-protein nitrogen of the perfusate.

It was felt that with the rapid withdrawal of sodium from the extracellular fluid, there was not a corresponding decrease in bicarbonate since the latter ion was, in a sense, forced to compete with chloride for diffusion. The excess of bi-

proportional to the volume flow of perfusion fluid and did not appear to vary perceptibly with the character of the solution as shown in Figure 3. The level of non-protein nitrogen in the perfusate was determined periodically and found to de-

cline at approximately the same rate as the urea nitrogen of the blood (Fig. 4). However, the blood creatinine continued to rise. Appreciable amounts of creatinine were found in the perfusate but accurate determinations were for some reason impossible. The continued rise in concentration of blood creatinine was never entirely explained. It is known that the normal renal excretion of creatinine in humans is mostly a glomerular but partially a tubular function. In intestinal diffusion this component of tubular secretion is probably lacking. The decreased rate of creatinine excretion cannot be explained on the basis of molecular size. Nonetheless, when the volume of urine flow had increased and the intestinal perfusion was eventually reduced and then discontinued the creatinine rose from 11.2 to 12.3 mg. while the non-protein nitrogen rose from 49 to 103 mg. It was this abrupt rise which caused us to reinstitute the perfusion operation.

We were constantly aware that disturbances in electrolyte balance were undoubtedly being produced. This became more apparent with the development of premature contractions and shortening of the phase of systole. Total serum calcium remained within normal limits, probably at the expense of its large reserve in the bones. No attempt was made to determine the value of ionizable calcium, but in the presence of an essentially normal concentration of blood proteins it was felt that the level of diffusible calcium was not abnormal.

With the administration of the large amounts of isotonic sodium in the perfusion fluid it seems likely that the concentration of sodium in the blood remained within the range of normal and that increased total body sodium simply increased the volume of extracellular fluid. Our greatest concern, however, was over the disturbance we were producing in the level of serum potassium, although one is accustomed to think of potassium as predominantly an intracellular cation and, therefore less likely to be affected by dis-

turbances in electrolyte balance. It is logical to assume that any alteration in the state of dynamic equilibrium which normally exists across the cell barrier by primarily depleting extracellular potassium, should secondarily lead to reduction of the intracellular potassium concentration. It has long been known that in uremia the serum potassium frequently reaches very high levels. In this instance it appeared probable that the reverse might be true, inasmuch as an undetermined amount of potassium was being withdrawn into the perfusate without being replenished save for the small amount administered in the daily plasma transfusion. This proved to be the case. Because of the difficulty of determining the concentration of potassium in the serum, no attempt was made to follow its level until the development of a cardiac arrhythmia made its determination a necessity. Accordingly, 12 hours before death, blood was withdrawn for the determination of potassium content but unfortunately the report was not obtained until after death. A level of 1.2 mEq./L. as determined by the flame photometer method is extremely low (normal 4.1 to 5.6 mEq./L.). Depression of potassium of this degree is consistent with the development of frequent premature contractions and sudden death.

Summary. The small intestine has been shown to be an easily accessible dialyzing membrane with the use of Miller-Abbott tubes. By means of massive perfusion flow the blood non-protein and urea nitrogen can be maintained at reasonably low levels in an anuric individual. Creatinine appears to diffuse through the intestine at a slower rate, permitting accumulation in the blood. It is believed, however, that increased levels of creatinine *per se* have a considerably lessened significance if nitrogenous and other wastes can be removed by extrarenal excretion.

No information was gained as to the removal of phenols, paraercsol, indican, guanidine, and others, felt by some observers to be responsible for the uremic

syndrome and the eventual cause of death. It is to be pointed out, however, that the patient looked well just before her sudden demise and presented none of the clinical signs of uremia. We believe that the extremely low level of serum potassium attained was the direct cause of death by inducing ventricular fibrillation. This should never again be encountered nor should the enormous difficulties in electrolyte, water and acid-base balance occur if electrolytically balanced solutions are used for perfusion. These fluids need not be sterile nor pyrogen-free and probably

can be prepared in the average hospital pharmacy in large quantities without too great difficulty.

At necropsy no important ill-effects appear to result from this form of therapy.

Conclusions. 1. A method of treatment of anuria by intestinal perfusion is presented.

2. A case is reported in which extrarenal excretion by intestinal perfusion was employed.

3. The problems encountered by this form of therapy are discussed.

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PROGRESS OF MEDICAL SCIENCE

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THE NORMAL RED CELL IN INFANCY AND CHILDHOOD; SOME RECENT ADVANCES

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This article attempts a condensed survey in sequential order of recent contributions to the understanding of the red cell in infancy and childhood. Attention is paid to structure, mechanisms of hemolysis, osmotic resistance as a measure of functional integrity of the cells, embryogenesis, and normal values and variations in the red count during infancy and childhood. More detailed expositions of some of the features can be found in the summaries by Maximow and Bloom²² (anatomy), Best and Taylor³ (physiology), Wintrobe³¹ (disease states), Ponder^{26a,b} (hemolysis), from whose descriptions the discussion of red cell structure has been largely compiled.

Structure. When examined in profile the red cells appear as biconcave discs with rounded ends and a constricted middle part, more marked on one side than the other. Considerable variations in diameter may exist between the smallest and largest cells.

The mean diameter is about 7.2 micra in dry films, and 8.0 in fresh wet states.³

The pale greenish-yellow color of the hemoglobin in the red cell is thickest at the periphery. In dense masses of cells the color turns into a distinct red. When the cells are lysed the hemoglobin is dissolved out into the plasma. The colorless corpuscle which remains is called a ghost or shadow cell, though as much as 30% of the original hemoglobin may still remain (Ponder).^{26a} The proportion of fixed stromal framework to hemoglobin appears to be about 3.4%.

Red cells are extremely soft and flexible. The slightest mechanical pressure such as may occur in passage through a fine capillary distorts their shape, but they return to the usual form as soon as the pressure is relieved.

Red cells possess a thin, semipermeable membrane composed of lipids and protein molecules. The membrane allows water and some water-soluble

substances to enter freely but is relatively impermeable to cations such as those of potassium and sodium. Under physiologic conditions the interior of the red cells and the plasma are in a state of osmotic equilibrium. If the molecular concentration of the plasma is lowered through the addition of water, water enters the red cell. If the osmotic pressure of the plasma increases, the red cell yields water to the plasma.

The evidence indicates that the surface membrane is a zone of assorted proteins and lipids only a few molecules thick. The interior of the cell possesses a sponge-like stroma of the same or similar materials, probably in the form of a gel. There is also an outer coating of "anti-sphering" protein, a fraction of serum albumin which can be absorbed away by glass. This protein layer aids in maintaining the discoid shape. When a cell suspension is placed between a glass slide and coverslip the shape becomes spherical. With plastic slides and coverslips this does not happen. Hemoglobin is held in the meshes of the stroma, or more likely is bound chemically to the stroma substance itself. The water content of the red cell is lower than that of most cells of the fixed tissues, amounting to about 60%. Hemoglobin makes up 80 to 90% of the total solids of the cell (and almost 34% of its fresh weight). Other proteins (0.5 to 1%), phospholipids (lecithin and cephalin) and cholesterol (0.4 and 0.3%, respectively), inorganic salts, urea, amino acid, creatine and trace amounts of other substances make up the remainder of the cell solids. Much of the lipid lies at or near the surface. Apart from hemoglobin the principal protein of the stroma is "stromatin" which in amino acid composition resembles the keratins. Potassium is the principal base.

The behavior of the red cell in solutions of varying osmotic pressures is

that of a colloidal system limited by a semi-permeable membrane rather than that of a membraneless gel. Not only does the law of isotonic coefficients hold for it, but the volume changes in solutions of varying concentration are in accordance with osmotic laws and not with those governing the swelling of gels. The fact that the cell body shrinks rather than swells as its pH is carried in the alkaline direction from the isoelectric point of its chief protein, hemoglobin, is indicative of an external membrane possessing differential permeability to ions.

The conceptions of the molecular structure of the surface membrane and the cell interior are still far from clear. Ponder^{26a,b} has summarized this controversial problem. It is likely that the stromatin protein forms a supporting intracellular matrix which is conjugated loosely with the hemoglobin mass. The discoid shape of the normal red cell results from the organization of molecules of surface and stroma, and is influenced also by the plasma albumin absorbed on the surface of the cell.

The usual stay of the mature non-nucleated red cell in the circulation is approximately 110 to 120 days (Mollison and Young,^{23a,b}). As the red cells age in the blood stream it is thought that they may become more spheroid and lose some elasticity, so that threading the small capillaries becomes mechanically more difficult. Old cells may fragment within the blood stream, or pass to oblivion in the recesses of the spleen. It is believed that in hemolytic processes the oldest cells are the first to be destroyed (Dameshek).^{7a,b}

The longevity of red cells is a relative matter, and depends upon environmental circumstances. The life span of red cells is determined by: (1) the intrinsic properties of the cell itself; (2) the activity of blood-destroying mechanisms which may or may not include the presence of a hemolytic proc-

css; (3) in the case of transfusion, the adaptation of this mechanism to the transfused cells. Transfused cells may disappear from the circulation at a regular rate indicating that the principal cause of death is old age, yet their life span may be much shorter than occurs in the original donor. The majority of red cells formed at one time die at the same time; some may be destroyed without regard to their age but old age seems to be the main factor which determines the life span.

(These generalizations regarding the structure of human red cells have been worked out without special reference to the factor of age of the subject.)

Hemolysis. The present status of the hemolytic mechanisms have been outlined in detail in Dameshek's recent reviews,^{7a,b 8a,b} with the provoking comment that more is known about abnormal blood destruction than about normal processes. Dameshek believes that no single mechanism can be incriminated as being solely responsible for all hemolytic states. Hemolysins defined as substances of any kind which directly or indirectly injure the red cell and lead to its destruction, are divided into two types: simple and complex. Simple hemolysins are chemicals such as saponin, lecithin, lysolecithin, arsine gas, benzol, and some of the sulfonamides or their end products. These cause the immediate destruction of the red cell without the intervention of any intermediate substance. Complex hemolysins, in contrast, injure the surface membranes as amboceptors, but do not actually destroy the red cells unless or until complement is added also.

Dameshek views agglutinins as being distinct from hemolysins, and much more common. Some agglutinins act at or above body temperature (warm agglutinin, e. g., the anti-Rh agglutinin), some act at any temperature, (e. g., the iso-agglutinins, anti-A and

anti-B), and some act best at icebox temperature, i. e., cold agglutinin. "Agglutinins may also be pure or simple in type, without any but an agglutinative action, or they may be more complex, i. e. act as agglutinins in one set of circumstances but as hemolysins under other conditions, e. g. when complement is added." In the absence of complement, agglutinins are believed to increase the fragility of the sensitized red cells to mechanical stress or strain. Stasis (Ham and Castle),¹⁶ splenic activity (Dameshek),^{7a} and physico-chemical changes in the environment must also be considered. An incomplete injury leads to spherocytosis, which is a change in shape indicative of partial hemolysis. Greater injury leads to escape of the hemoglobin, and perhaps to complete destruction of the cellular structure itself.

It is generally believed (Haden,¹² Ponder^{26a,b} Dameshek^{7a,b}) that save for a few exceptions, the shape changes which initiate and accompany the breakdown of a red cell follow substantially the same pattern no matter what the hemolytic agent. The first change, according to Ponder, is the appearance of small discrete irregularities on the discoidal surface, believed to indicate a focal reaction of the hemolytic agent with molecular groupings of the cell membrane. As hemolysis progresses the number of crenation points increase until the entire surface is thickly studded. At the same time the cell tends to become spherical. The crenations become more numerous and finer and finer, and soon are no longer recognizable. The cell then has the appearance of a glistening sphere with a smooth surface. During the first phases of this process, hemolysis may be prevented by washing off the saponin or adding normal serum which neutralizes the hemolytic action of this and many other substances. The red cell may then return to its original shape. But if the hemolysins are per-

mitted to act until the discoid cell has grown smooth and round, the process becomes irreversible and the distended red cell fades rather suddenly from the microscopic field. During the stage of fading it is known as the "prolytic" sphere. The hemoglobin flows out rapidly through the open pores and only a gossamer-like "ghost" remains.

Ponder's direct microscopic studies of the changes in form which take place during hemolysis have led him to hypothesize that two cell components are involved in lysis. The first is concerned with mechanical rigidity and maintenance of the biconcave shape. The second is concerned with the prevention of the outward diffusion of hemoglobin. Some lysins such as lecithin seem to act on the "rigidity component" much more rapidly than on the "permeability component," whereas other lysins such as saponin produce their effects on the two components more nearly simultaneously. "To give the terms a definite, if temporary, meaning, we may think in the meantime of the shape component as being a supporting ultrastructure, probably, but not necessarily, situated at the surface of the cell, and of the permeability component as being a layer or membrane, only a few molecules thick, situated somewhere in the thickness of the ultrastructure."

The ionic and osmotic equilibria which attend the red cell in various media, and particularly plasma, have interested many workers, and a large body of literature has been built up. The most recent report is that of Jacobs and Stewart.²¹ These authors summarize some of the earlier work and propose a mathematical formula to treat with all theoretically possible cases. This formula deals with the many different combinations inside and outside the cell of penetrating and non-penetrating anions, penetrating and non-penetrating cations, penetrating and non-penetrating neutral molecules,

and proteins. "Even with the necessary restrictions that there must always be an electrical balance between anions and cations and that every penetrating ion and molecule must be represented at equilibrium on both sides of the cell boundary, they number several hundred."

Jacobs and Stewart²¹ point out that only the problems of the anions in relation to red cell permeability have been studied to any great extent. The surface membrane is freely permeable to most anions (the citrate ion is a prominent exception), and therefore "its continued existence in a salt solution is dependent upon either a physical or physiological (Harris)¹⁷ impermeability to cations. Without restraining forces of a magnitude greater than those believed to be present, a simultaneous permeability to both anions and cations would be incompatible with the preservation by the cell of its normal volume. Consequently any agent that makes erythrocytes permeable to cations should have hemolytic properties. A good example of such an agent is *n*-butyl alcohol (Netsky and Jacobs)."²¹ This general type of hemolysis, known as colloid-osmotic hemolysis, has been recently investigated by Willbrandt,²⁰ who has shown it to be of frequent occurrence. Colloid-osmotic hemolysis can be prevented or greatly retarded by low concentrations of non-penetrating non-electrolytes like sucrose. Jacobs and Stewart believe simple osmotic principles can account for colloid-osmotic hemolysis and other puzzling phenomena, such as the hemolytic effects of ammonium salts and their inhibition by addition of sufficient sodium chloride solution.

Findlay¹¹ points out that in hypotonic saline solution, the escape of hemoglobin from the swollen red cells appears to be by diffusion through the cell membrane, leaving the stroma and cell membrane pale but still recognizable. Distinction must therefore be

drawn between hemosmosis (escape of hemoglobin) and stromatolysis (disintegration of the cell body).

One hemolysin present in trace amounts in normal blood serum is lysolecithin. Lysolecithin was used by Singer²⁷ as a means of testing red cell fragility. Normal cells showed incomplete hemolysis at a lysolecithin dilution of 1 to 16, whereas the cells of congenital hemolytic jaundice showed complete hemolysis at this dilution. Singer noted that some patients whose red cells exhibited a normal saline fragility had a rapid lysolecithin reaction. In a few patients with sickle cell anemia there appeared to be a lack of parallelism between the resistance of the red cells toward hypotonic saline as compared with lysolecithin.

Osmotic Resistance. The fact that the integrity of the red cell becomes abnormal in certain diseases has led clinicians to search for such an abnormality when the presence of these diseases is suspected in their patients. The most widely employed test for disturbed cell structure is that of "fragility," in which small quantities of the blood under investigation are distributed through a graded series of hypotonic aqueous solutions of sodium chloride. This test has a sound theoretic foundation, as will be brought out in succeeding paragraphs. Unfortunately the recommendations for the procedure given in most texts on clinical pathology fail to control several crucial variables. In Fennel's¹⁰ phrase, "our methods of investigation have been about as simple and accurate as tickling a flea in the ribs with a telegraph pole."

Hypotonic salt solutions are, of course, but one kind of abnormal environment. Of as great or greater potential value for information are solutions containing thiourea, glycerol, lysolecithin, urea, ethylene glycol, or other penetrating or non-penetrating organic and inorganic substances. Alterations in osmotic resistance can be

found more or less regularly in congenital ictero-hemorrhagic anemia, Mediterranean (Cooley's) anemia, and 2nd sickle cell anemia. It is obvious, of course, that interpretations of findings in abnormal states depend on the values for the normal and the ranges of normal variation.

One must always bear in mind that the osmotic approach deals not with single red cells but with population samples composed of many millions of units. These populations are far from homogeneous with respect to osmotic resistance. Curves of percentage susceptibility become apparent when blood specimens are distributed through appropriately graded series of testing solutions. Thus when destructive cell rupture is taking place in a red cell suspension, the rate of liberation of hemoglobin or diminution in turbidity can be measured by optical methods. Differential curves will be exhibited, with units of time as ordinates and percentages of hemolysis as abscissas. It is probable that in normal blood the most fragile cells which rupture first are the older cells, with reticulocytes and younger cells the last to go.

Jacobs and Parpart^{20a} have ascribed the osmotic variability in red cell populations to probable chemico-structural differences in the membranes of different cells, either in resistance to stretching or in becoming permeable to hemoglobin when stretched. They comment that the quantity of cells in a population being tested is so numerous that successive samples from the same lot of blood prove almost identical. The osmotic variations are practically continuous and represent an almost infinite number of degrees of hemolytic resistance. The variability of the cells instead of being a source of error becomes an advantage, by rendering it possible to compare with a high degree of accuracy the osmotic properties of solutions whose concentrations differ but slightly.

Many experiments on the osmotic

behavior properties of red cell populations have been carried out by Jacobs and his associates.^{18a, b, 19, 20a, b, c, 21} With penetration by water alone, the noted changes are an exact measure of the amount which has entered or left the cell. With solutions of dissolved substances conditions are somewhat more complex. When a dissolved substance enters a cell in osmotic equilibrium with its surroundings an osmotically equivalent amount of water accompanies the entering solute. If the cell does not oppose the resulting tendency to swell by means of a resistant membrane or otherwise, and if water penetrates as rapidly as the dissolved substance so that osmotic equilibrium is at all times maintained, then the increase of volume may be used as an accurate measure of the amount of substance which has penetrated.

Unfortunately, it is not practicable to observe with accuracy the volume of individual red cells. The hematocrit technique which measures the aggregate volume of a very large number of cells tightly packed together has certain disadvantages, the most important being the time required for accurate volume determinations. The hematocrit technique can be employed only with substances which penetrate slowly. For this reason Jacobs^{18b} favors the indirect method, which measures the decrease in turbidity in the red cell suspension as the cellular integrity is destroyed. This approach assumes that when the red cell swells to a certain fairly definite volume its hemoglobin escapes—if not wholly at least to the extent that the cell becomes invisible in its hemoglobin-containing surroundings. One great advantage of the hemolysis method over the hematocrit method is that it is adaptable to experiments of only a few seconds total duration.

The speed of hemolysis depends upon the rate of entrance of the dissolved substance, the rate of entrance of water, and the rates of escape of

the hemoglobin, the salts, and the other osmotically active substances. It is not solely a measure of the rate of penetration of the dissolved substance, though in controlled circumstances it may be. One source of error may be the non-osmotic effect of the penetrating substance. In addition, osmotic hemolysis is favored by lower temperatures and inhibited by higher temperatures, and is extremely susceptible to changes in the environmental pH. Alterations in oxygen tension can give rise to secondary osmotic effects. All these environmental factors must be carefully controlled if valid conclusions are to be drawn from fragility experiments.

Guest and Wing¹⁴ describe hematocrit measurements in parallel of the swelling and hemolysis of red cells suspended in hypotonic salt solutions. The subjects were 3 normal newborns, 5 normal infants and children and 7 adults. They concluded that their data supported the thesis of Ponder and others that red cells within certain limits behave as perfect osmometers. There was close agreement between values for "expected osmometric swelling," and for the cell volumes determined at each tonicity. The thesis of Haden¹⁵ and others that the maximum swelling of red cells is limited by an inelastic surface membrane was supported also by the close agreement found between values for the expected maximum swelling calculated from the mean surface area of the cells and the maximum cell volumes actually determined.

These authors¹⁴ suggest as possibly fallacious that 10% hemolysis as measured by the amount of hemoglobin in the supernatant fluid represents the rupture of the identical percentage of cells in the sample; this amount of hemoglobin would not represent the same proportion of cells if derived all from small cells or all from big cells. It is conceivable also that some more resistant cells may lose part of their contents without full rupture. Further-

more, if salts escape from some cells more easily than from others, this would lead to less swelling if occurring before the peak, or to shrinkage when the cells are swollen to the maximum.

The most important factor theoretically and the most difficult one to control practically is the pH of the medium. Jacobs and Parpart^{20a} state that more errors have been caused in osmotic hemolysis studies by neglect of this factor than of any other. When a relatively large quantity of blood is used with an unbuffered salt solution, the resulting pH will be determined chiefly by that of the blood. This in turn will vary greatly according to the amount of CO₂ which has been allowed to escape. If very small quantities of blood are employed the situation is no better. The final pH will be strongly influenced by that of the solutions used. Adsorption of CO₂ from the laboratory air in the absence of buffer may be expected to vary considerably. A breath from the experimenter at the wrong time may completely ruin an experiment.

Reference must be made to the minute traces of silver often present in so-called chemically pure sodium chloride.¹ These traces come from the use of silver-lined vessels in the purification process. Since silver is hemolytic, specially prepared silver-free sodium chloride should be used in the preparation of saline solutions for hematologic work. (Silver-free sodium chloride can be obtained from Merck and Company.)

Apparently insignificant changes in environmental factors such as pH and temperature produce osmotic effects within the red cell of a magnitude sufficiently great to make it impossible to secure reproducible results by a method as sensitive as that of hemolysis. "If it be true, as appears to be the case, that pH changes of 0.01 pH unit and temperature changes of 0.5 C. can produce measurable osmotic effects, what

is to be said of the numerous papers which have been published upon the "fragility" of the erythrocytes under almost all conceivable normal and pathological conditions, in which in the absence of any information whatever concerning these factors an uncertainty of as much as 2.0 pH units and 10 C. or more may exist and in which, in addition, there is frequently no assurance that the experiments have been sufficiently long continued to secure approximate equilibrium? The erythrocyte being what it is, attempts to use it for comparative osmotic studies without controlling especially the factors pH and temperature and to a lesser extent oxygen tension, are scientifically in the same category with attempts to study volumes of gases without accurate regulation of temperature and pressure" (Jacobs and Parpart).^{20a,b,c} To obtain reproducible results in osmotic resistance studies, one must use very small quantities of blood well shaken into buffered solutions of known pH at a constant temperature.

Creed⁴ has published confirming experiments. He found cells of venous blood to be more fragile than those of capillary blood, and noted that this difference in fragility could be abolished by exposing the blood to a current of air before adding hypotonic saline. The longer the tourniquet was applied and the greater the cyanosis the more fragile the red cells. For consistent results the aeration must be thorough, as by blowing a strong current of air over it for 4 minutes. In addition with saline fragility tests the ratio of blood to saline must be kept constant, to avoid discrepancies from the varying quantities of plasma introduced. The increased proportion of plasma in a drop of anemic blood makes its corpuscles appear less fragile. One drop to every 25 drops of saline gives sufficient color for matching purpose, even with anemic blood.

Creed advised that whole blood

rather than washed corpuscles be used in fragility studies in order to retain the buffering effect of the plasma. If washed corpuscles are used slight alterations in pH of the hypotonic saline will produce gross alterations in fragility of the washed cells. He noted also that hemolysis by hypotonic saline was rapid, and practically complete within 5 minutes. No further hemolysis occurred for some hours. It was immaterial whether the tubes were centrifuged after 20 minutes or 6 hours; but the centrifugation and pipetting off of supernatant fluid and washing of deposit with saline should be completed the same day, as further hemolysis may occur on standing overnight, even in a refrigerator.

Dacie and Vaughan⁶ likewise have described parallel studies with conclusions essentially similar to those of Creed⁴ and Jacobs^{18a,b}. They utilized the ratio of mean corpuscular thickness to median corpuscular fragility (which is a measure of how far a red cell diverges from the spherical form) as the expression of cell size most likely to be linked with red cell fragility. Increase in this ratio is usually though not necessarily associated with an increase in fragility. The authors emphasize that when the temperature of a hypotonic solution is lowered hemolysis is promoted, and vice versa. They attribute this to a loss of osmotically active substances and associated water with rise in temperature, resulting in the cell becoming smaller. Cells suspended in a warmer medium being smaller are able to take in more water before rupturing and hence appear more resistant. An alteration of 2° C. in the temperature of the saline solution used for hemolysis was equivalent to about an 0.002% alteration in saline concentration. They noted also that alterations in fragility produced by variations in O₂ and CO₂ content of blood were most marked in association with anemia. The more anemic the blood the less fragile the

cells appeared. At least 2 factors may explain this alteration in fragility: variation in the amount of added plasma, and oxygenation. When a drop of blood is added to 1 cc. of saline solution the effective salt concentration is raised because a certain amount of plasma of ionic concentration 150-166 meq. per liter (about 0.90% NaCl) is added. The more the plasma contained in any drop (as in "anemic" blood) the greater is the osmotically equivalent sodium chloride concentration of that drop and the higher the resulting salt concentration of the plasma-saline hemolytic mixture. The effect of the added plasma can be demonstrated by performing several fragility estimations on the same specimen of blood, employing different quantities in each case. Increasing the amounts of blood added to equal volumes of saline increases the resistance to hemolysis. As for the oxygen-carbon dioxide relationships, the escape of carbon dioxide results in a profound alteration in the plasma pH if CO₂ is permitted to escape at the same time. The loss of CO₂ is associated with an ionic shift which results in an osmotic loss of water. This loss of water and anions reduces the mean corpuscular volume, which becomes reflected as an increased resistance to hypotonic hemolysis.

Chemical differences at present unrecognized in different types of anemic red cells may also be responsible for differences in response to hemolytic solutions. The importance of chemical constitution is emphasized by the fact that in familial acholuric jaundice following splenectomy red cell fragility may remain increased whereas thickness returns to normal. Observed red cell fragility is decreased in anemia, apart from any fundamental variation in cell size and shape. In performing fragility estimations it is essential to consider the degree of anemia which may be present.

All workers in the field are aware

that the current method of reporting hypotonic fragility as commencing at one dilution and being complete at another is far from satisfactory (Creed,⁴ Dacie.⁵) The points at which fragility is adjudged to start and finish depend on the care with which traces of hemolysis, or of incompleteness, are sought for. Furthermore, within these limits the curves which represent the extent of hemolysis in the successively diminishing strengths of saline are not necessarily equal or even similar with respect to different individuals, whether sick or well.

In congenital hemolytic jaundice agreement is general that the red cells have a spherical shape, with mean cell diameter decreased, volume thickness index increased, and mean corpuscular volume variable. In simple microcytic anemia the index is normal; in obstructive jaundice the index is decreased since the mean diameter is usually increased without a corresponding rise in mean corpuscular volume.

Though microspherocytosis and increased fragility are the most constant features in congenital hemolytic jaundice, no one has proved a direct relationship between these two phenomena. Haden¹⁵ believes that the increased fragility is related to and dependent on the spherocytosis. There is a close relationship between the point of initial hemolysis and the volume-thickness index. In the severe case of congenital hemolytic jaundice with a high volume-thickness index and a marked tendency to a globular form, very little dilution is possible before hemolysis begins. The cells in this disease may be regarded as nearer the hemolysis point by reason of their shape.

In patients with congenital hemolytic jaundice, Dameshek and Schwartz^{8a,b} studied the fragility in relation to red cell count, red cell size, and reticulocyte percentage. They too noted a striking correlation between spherocytosis and increasing fragility in hypo-

tonic salt solution. The red cells were unusually susceptible to hemolysis when the average diameter was reduced and the average thickness increased. With increasing cell diameter and diminishing cell thickness the cells' resistance to hemolysis became more marked. When there was a "pseudomacrocytic" blood picture with reticulocytes as the outstanding cells, the red cells were actually more resistant than normal. This spherocytosis is believed by Dameshek and Schwartz to indicate the presence of some hemolytic agent; the shape is more than an anatomic peculiarity.

Dameshek and Schwartz^{8a,b} studied the mechanism of hemolysis in three successive cases of acute non-familial hemolytic anemia associated with active serum isohemolysins in the circulation capable of hemolyzing red cells of their own type and of Group O. They also investigated the effects in guinea pigs of hemolytic serum prepared by injection of guinea pig red cells into rabbits. In both situations an outstanding feature was the development during the hemolytic phase of a large number of small thick red blood cells (spherocytes), possessing a greatly increased volume thickness index and increased fragility. In the experimental hemolytic syndromes the number of spherocytes varied directly with dosage of hemolytic serum; i. e., the larger the dosage, the greater the number of spherocytes. The nucleated red cells of the peripheral blood were always normal in size and nucleated microcytes were never encountered. Normal also were the red cell diameters of the most mature nucleated red cells in the bone marrow of animals dying with almost total microspherocytosis of the peripheral blood.

Dameshek and Schwartz conclude that: (a) spherocytes are formed outside of the bone marrow; (b) spherocytosis develops only in mature red cells; (c) a hemolytic agent such as is

present in hemolytic sera is responsible for their development. Doubt is cast on the idea that spherocytosis is pathognomonic for congenital hemolytic jaundice and indicative of an inherited bone marrow defect. It is suggested that the extreme spherocytosis during crises in this disease may be due to the sudden liberation of large amounts of hemolysin with resultant action upon the mature red cells. Bessis² has described somewhat parallel observations in rats given injections of anti-rat red cell serum prepared by immunizing rabbits against rat red cells.

Findlay¹¹ surveyed the literature dealing with the resistance of the red cell in infancy and childhood to hypotonic solutions of saline and uncovered a great divergence of opinion. Some authors believe that the resistance of the red cell to hypotonic saline in the fetus and newborn child is diminished in comparison with what obtains in adult life; some believe there is no difference in this respect; others hold that the resistance is normal at birth, increases during the first few days of life to reach a maximum about the fourth day, and then gradually returns to the adult level. Findlay points out that hardly any 2 workers have employed the same method and practically all have failed to take into account factors which are now generally admitted to have a critical influence on osmotic resistance. Using Creed's technique in which CO₂ concentration and the relative amounts of cells and plasma are brought to a uniform level, Findlay found the resistance of fetal blood to be slightly diminished and that of the infant and child to be slightly increased.

This survey of recent contributions on the structure and osmotic behavior of red cells leads to at least one major conclusion. The osmotic resistance test as a diagnostic aid will give maximum information only when the theory and mechanisms are well understood by the

user, and then only if the many technical variables which can give rise to false positive readings have been kept under rigid control.

Embryogenesis. A survey of red cell development in the human fetus has been assembled by Windle.³⁰ Formation of red cells begins in the wall of the embryonic yolk sac shortly after formation of the germ layers, and continues there until the second month. Blood formation begins to shift to the body mesenchyme and blood vessels at about the fifth week. In the following week, the liver starts to produce red blood cells; it soon becomes the most active erythropoietic organ and remains so until midfetal life. Erythropoiesis is initiated in the spleen at the end of the second month, and in the bone marrow during the third month. The activities of the various organs overlap and most foci of erythropoiesis are transient. Formation of blood elements outside of the bone marrow ordinarily stops at birth.

Most investigators hold that the various blood elements arise from a common ancestor, a generalized mother cell, often called a hematocytoblast or hemoblast. This is a large ameboid element resembling a large lymphocyte. Differentiation of the red cells proceeds through proerythroblasts, erythroblasts, normoblasts and reticulocytes. Proerythroblasts show the first traces of hemoglobin in their cytoplasm, and are the only "red" cells to develop in the first 6 weeks; after the third month they are confined to the hematopoietic centers. Erythroplasts or true red cells arise from normoblasts by fragmentation and extrusion of their nuclei. They make their appearance as spherical forms in the liver at about 2 months and become the predominant hemoglobin-containing element of the blood during the third month of fetal life.

At 3 months approximately 90% of

the red cells are reticuloocytes. The proportion of reticuloocytes diminishes rapidly to from 15 to 30% at 6 months and to only 4 to 6% at birth. About 0.1% normoblasts are found at birth; other types of nucleated cells are not normally present.

The number of red cells in the circulating blood increases from less than 400,000 per c. mm. at 5 weeks to approximately 3.5 million per c. mm. at 6 months. The amount of hemoglobin is 10 gm. per 100 c.c. of blood in the fourth month of fetal life, increasing gradually to the birth level.

Fetal red cells are larger than those of the infant after birth, and exhibit wide variations in size. The average diameter of corpuscles at 3 months gestation has been reported to be 9.2 micra and at 6 months 8.1 micra in the dry state (smears). As the increase in the number of red cells during development of the fetus is much more prominent than the progressive decrease in corpuscular size, hematocrit values rise as gestation proceeds toward term.

The full-term fetus does not possess a polycythemia ascribable to the comparative lack of oxygenation of its circulating blood. At the end of prenatal life there are actually fewer red cells per unit volume of blood than in the adult. Fetal hemoglobin values at term are in excess of those encountered in the normal adult, associated with the larger size of red cells in the fetus than in the adult. Special anatomic and mechanical mechanisms enable the fetus to obtain oxygen with greater avidity in a placental environment of relatively low oxygen tension and without the necessity for developing an excessive number of red corpuscles. It seems probable that the stimulus to blood cell development in uterine life comes from intrinsic, perhaps hormonal, growth factors, rather than in response to oxygen unsaturation.

Gilmour's¹² detailed histologic exam-

ination of normal hemopoiesis in intra-uterine and neonatal life is in accord with Windle's general picture.

During the differentiation of the erythroblasts the nuclei show all gradations of diminution in size, condensation of chromatin structure, and contraction in size and number of nucleoli from that of the hemocytoblast, till eventually the nucleus becomes shrunken and pyknotic. The pyknotic nucleus is then extruded and the cell becomes a mature red cell. During early development, erythroblasts multiply by mitotic division. In late development they probably do not multiply and those with pyknotic nuclei certainly do not.

The stage of development of the erythroblast at which visible hemoglobin appears varies, giving rise to the recognition of 2 routes of red cell formation. In one type hemoglobinization is late and begins in small erythroblasts with pyknotic or almost pyknotic nuclei. This is termed normoblastic erythropoiesis. In the other type, hemoglobinization occurs in larger erythroblasts with larger nuclei having still a well-preserved nuclear structure. This is termed megaloblastic erythropoiesis. In early embryonic life normal erythropoiesis is entirely megaloblastic. In fetal life it is increasingly normoblastic and decreasingly megaloblastic. After the first 2 or 3 weeks of post-fetal life normal erythropoiesis is entirely normoblastic.

In the series of early human embryos described by Gilmour¹² the erythroblasts were first detectable in a presomite embryo (2.5 mm.) within the blood islands of the yolk sac. These were megaloblasts derived directly from hemocytoblasts. With the establishment of the circulation the premature erythroblasts entered the embryonic vessels and continued to multiply there. With increasing age the number of early and intermediate premature erythroblasts decreased and the late and

pyknotic late forms and megalocytes increased, accompanied by diminished multiplication. Mitotic division of primitive erythroblasts had ceased in the 35 mm. embryo. In the 48 mm. embryo these cells were all in a late or pyknotic late stage. In older embryos no primitive erythroblasts were recognizable in the blood but primitive megalocytes undoubtedly persisted longer. In embryos of 3 to 35 mm., multiplication and development of primitive erythroblasts continued in places in many connective tissues, the original cells having reached the tissues by hemorrhage. In the 35 mm. embryo most of these cells had developed into megalocytes and the erythroblasts were all late. Erythropoiesis appeared first in the 10 mm. embryo in the yolk sac vessels as groups of primary erythroblasts and megaloblasts. Hemocytoblasts had appeared among the hepatic and yolk sac epithelial cells in the 10 mm. embryo but extravascular definitive erythropoiesis did not begin until the 12 mm. embryo and, in the yolk sac, till the 15.5 mm. embryo. In the liver it increased in amount and reached a maximum relative to parenchyma in the 26 mm. embryo. The maximum persisted until in fetuses of 200 to 457 mm. there was a progressive decrease to a slight amount which remained constant in fetuses of 470 mm. and more. In infants 5 or more days old such erythropoiesis was absent. In the spleen erythropoiesis in the pulp and to a lesser degree in the sinuses began in the 70 mm. embryo and disappeared in infants over 5 days old. In the connective tissue of the marrow erythropoiesis first began in the clavicle in the 57 mm. embryo and subsequently increased considerably in amount. In the blood megaloblasts were present in small numbers in the 28 and 35 mm. embryos and were almost as numerous as the primitive erythroblast in the 48 mm. embryos. In fetuses of 76 to 146 mm. there was

exceptional erythropoietic activity in the blood. After the 15th day of life erythropoiesis was confined to the marrow.

Normal Values and Variations in Infancy and Childhood. A number of careful studies are on record describing red cell counts in early infancy. The variations are great. The figures vary from those encountered in normal adults to average values as high as 6.5 million red corpuscles per c. mm. Individual counts greater than 7 million are not uncommon. Windle³⁰ comments that these differences are too great to be accounted for as the basis of normal race or individual variations, and believes that they depend on differences in the sites and methods of collecting. Authors seldom state whether the blood was drawn from infants allowed to retain their placental blood or from those deprived of it by immediate clamping of the umbilical cord at birth, and seldom give the time interval lapsing since the moment of birth.

The number of red cells in a cubic millimeter of umbilical blood at the end of gestation, according to Windle, is lower than 1 hour after birth. The average differences amounted to 1 million red cells in 25 infants whose cords were clamped immediately at birth, and to more than 1.5 million in 25 whose cords were not clamped until placental blood had passed into the infants at birth. Corresponding hemoglobin differences were encountered (3 gm. in immediate clamping and 6 gm. in the delay group). It is doubtful that this sudden increase is due to a difference between capillary and venous blood, since blood obtained from the superior sagittal sinus (or jugular vein) and from the heel capillaries in 6 normal infants showed no significant difference with respect to the number of red corpuscles. Postnatal dehydration seems an unlikely explanation because the increase may take place in less than

half an hour. A possible cause is splenic contraction, with expulsion of stored red cells into circulation.

Similarly, Findlay¹¹ studied 11 newborns of varying degrees of maturity in whom the hemoglobin and red cell concentrations increased after birth. The increase within the first few hours of life in both hemoglobin and red cells varied from 13 to 70%, and in the hematocrit readings from 10 to 75%. Thus it would seem that there is a call for more oxygen carriers rather than for fewer during the critical neonatal periods. Findlay believes that this phenomenon represents an increase in concentration of the blood, though the increase in concentration is much greater than what could occur from a dehydration taking place after birth. The loss of 1 pound (which would be an abnormally high figure and in any case would be spread over 2 or 3 days) should effect a change in hemoconcentration of only 12%, whereas the increase actually observed during the first hours of life may be as great as 70%.

De Marsh, Alt, and Windle⁹ clamped the umbilical cords as soon as possible after normal delivery without anesthesia in one series of 25 healthy newborn infants; the elapsed time was 30 seconds or less. In another 25 infants the cords were not clamped until the placentas had separated from the uterus, which usually occurred about 10 minutes after delivery. The additional amount of blood received by the baby from the placental vessels was measured in 10 instances and found to average 62 cc. The average values for cord blood were 4.5 million red cells per c. mm. and 15.7 gm. of hemoglobin per 100 cc. These were approximately the same whether the cord was clamped early or late. Within 20 to 75 minutes after birth the values in blood from the heel were much higher, as already described. Thenceforth those infants whose cords were clamped immediately had significantly

lower red counts and hemoglobin values than those whose cords were clamped late. During the first week, the former group averaged 5.45 million red cells per c. mm. and 19.5 gm. of hemoglobin per 100 cc., whereas the latter group averaged 6.01 million red cells and 22.1 gm. of hemoglobin.

Most observers have reported the reticulocyte count at birth to average about 4 to 6%, decreasing rapidly to less than 1% at the end of the first week. De Marsh, Alt and Windle⁹ compared reticulocyte values in 6 infants whose cords were clamped immediately and in 6 whose cords were clamped after delay. When the cord was tied immediately, reticulocytes reached an average peak of 8.6% at 24 hours and did not fall below 6% until the fifth day. When tying of the cord was delayed, reticulocytes averaged only 5.8% at their peak in 24 hours and fell to 4% in 48 hours. A more active blood formation when the cord is clamped early than when it is clamped late is suggested by the higher and more sustained rise in reticulocytes in the former group.

Deprivation of the newborn infant of its placental blood may contribute to iron deficiency in infancy. The principal iron reserve of the newborn infant lies in the circulating hemoglobin. Iron liberated during neonatal blood destruction is stored in the tissues and utilized as needed for hemoglobin formation. The amount of iron lost to the newborn infant when 100 cc. of placental blood is prevented from reaching the child is 54 mg. This is enough iron to lower the hemoglobin in a 4 month old infant from 12 to 9.3 gm. per 100 cc. of blood. It seems likely, therefore, that loss of placental blood may be important in predisposing infants to anemia during the nursing period.

Findlay¹¹ criticizes the usual assumption that immediately after birth a hemolytic destruction of blood takes place to correct for the greater amount

of oxygen provided by external respiration, with resulting jaundice. Findlay argues that expansion of the lung is not a sudden event with rapid availability of the alveolar surface, but occurs gradually over several weeks. Furthermore, following birth the child is deprived of the extra-medullary hemopoietic tissue on which it was chiefly dependent during fetal life. The newborn infant has need to conserve its red cells, at least until respiration is fully established and medullary hemopoiesis is well under way.

Since the drop in hemoglobin and red cell levels is more marked during the second than during the first week of life, it is unlikely that this drop plays the chief role in the production of icterus neonatorum which usually sets in on the second or third day of life. The fact that there is little or no difference between the rates of fall in icteric and non-icteric infants renders such an association still less likely. In fact, studies on the blood of 20 newborn infants revealed a slightly greater fall in the total amounts of hemoglobin and red cells in those infants who failed to exhibit jaundice.

Findlay found that one of the most marked alterations in the change-over from fetal to natal life was the diminution in size of the red cell and its content of hemoglobin. Immediately after birth there occurs a marked diminution in both mean corpuscular volume and mean corpuscular hemoglobin content, but no alteration in the mean corpuscular hemoglobin concentration.

Parsons²⁵ has compared the Price-Jones curves of premature and full term children. These are similar during the first few weeks of life, and show a megalocytic type of curve with a greater degree of anisocytosis than occurs in older children or adults. In the second week of life the curves show little change except that the mean diameter of the red cells increases a little. During the third and following weeks, the curves of premature and full term

children separate, the mean diameter of the red cells decreasing in the premature children, and anisocytosis being more marked. The mean diameter of the red cells in premature children reaches its smallest figure at the age of 8 weeks. After the tenth week, a slow increase in the mean diameter occurs and anisocytosis slowly becomes less. In full term children the mean diameter of the red cells decreases in the fifth week and remains about constant from the sixth week onwards and anisocytosis becomes definitely less. Thereafter the curve approaches more and more the adult type. At about the eighteenth to twentieth week the Price-Jones curves of premature and full term children become identical again.

Guest, Brown and Wing¹⁴ have presented data on the number, size and hemoglobin content of the red cells in 615 infants and children ranging in age from birth to 5¼ years. Of interest are their observations on mean red cell size. In 34 samples of blood from the umbilical cord the mean red cell size was 113 cubic microns. This fell immediately after birth. At 8 months the average value was 73 cubic microns and about 72 cubic microns in the first half of the second year. At about the age of 8 months, values below 70 cubic microns began to appear with increasing frequency. At 9 months the tendency toward lower values was more pronounced. Microcytosis continued frequently through the second year. After the second year the scatter in the values for red cell size diminished rapidly. Average values at 3 and 4¼ years were 78 and 80 cubic microns respectively.

As another example of recent studies of normal blood in infancy and childhood, one may cite the data of Gil-mour.¹² The quantity of hemoglobin, the number of red blood cells, and the volume of packed cells were determined in 533 children ranging in age from birth to 13 years. Differences between boys and girls were not signifi-

cant. The highest mean hemoglobin value 17.14 ± 0.16 gm. was found in the blood of the cord. The lowest mean value, 11.14 ± 0.15 gm. occurred between the ages of 2 and 4 months. Infants between the ages of 4 and 8 months showed an increase to a mean of 12.29 ± 0.12 gm. Lower values were again found in the period between the eighth and eighteenth month, with the low mean of 11.73 ± 0.11 gm. occurring between the twelfth and eighteenth months. From the age of 18 months there was a gradual increase to the mean of 14.49 ± 0.09 gm. at 12 years, which is the approximate mean value for normal adults.

From a mean of 4.88 ± 0.04 million per c. mm. in the blood of the cord the red cell count fell to a low mean of 3.9 ± 0.06 between the ages of 2 and 4 months. There was a fairly steady increase from this age period up to the age of 12 years when the mean is 4.66 ± 0.02 million.

The mean value of packed cells of cord blood was 53.18 ± 0.5 cc. per 100 cc. of blood. The low mean of 34.18 ± 0.4 cc. appeared in the period between 2 and 4 months. The mean was slightly higher between 4 and 8 months than in the period up to 18 months. After 18 months the mean value showed a progressive rise to the mean of 43.15 ± 0.19 cc. at 12 years.

As in other studies the large size of the red cells at birth and in the first days of life was noted. In corpuscular volumes the highest mean of 180.9 ± 0.55 cubic microns appeared in the blood of the cord. The large size persisted through the first few days of life. Toward the end of the second month the cells were considerably smaller. The decrease in corpuscular volume continued to the low mean of 85.3 ± 0.35 cubic microns between the ages of 12 and 18 months. An increase in volume began after the 18th month and the mean for adults was approximated in the third year.

Washburn²⁸ has paid particular attention to the postnatal adjustments, studying 15 healthy infants during the first 10 to 18 weeks of life. As the total body mass increases rapidly—up to as much as 50% in 6 weeks or 100% in 14 weeks—a proportional increase in total blood volume presumably also occurs. To maintain the number of red cells per unit volume of blood at constant level the infant would have to manufacture new cells considerably faster than ordinarily needed. Most infants show an abrupt drop in their reticulocyte count to from 0.2 to 0.8% postnatally. If the normal maintenance of the red cell level is reflected by the presence of about 0.8 to 1.2% reticulocytes, then most infants are not manufacturing new cells fast enough to maintain a constant level of red cells even if there were no great increase in blood volume. As long as the body weight continues to rise and the reticulocyte percentage to remain low, the red cell count, the volume of packed cells and the amount of hemoglobin must necessarily decrease. The more rapid the increase in total body mass, the more rapid the decrease in the number of cells per cubic millimeter of blood. Eventually the decreasing concentration of red cells and hemoglobin leads to stimulation of the hemopoietic tissue, most simply conceived of as resulting from lack of oxygen. The decrease in the red cell count and level of hemoglobin evokes a rise in reticulocytes at the 5th to 8th week. The sharpness and persistence of the rise varies roughly with the rapidity of weight gain and the speed of decrease in red cell count. When the number of red cells per cubic millimeter of blood has reached an optimum level for the body economy, the reticulocytes return to an approximate maintenance level of about 1%, the exact level depending upon the individual baby and even varying from time to time in the same infant.

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GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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"ROOMING-IN"

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"Rooming-in" is a term applied to a maternity hospital plan which permits newly born infants and their mothers to room together during the lying-in period. Such a natural arrangement is, of course, inherent in domiciliary obstetrics. Its features have traditionally been preserved in the planning and practices of maternity institutions abroad. In maternity hospitals in this country, on the other hand, the prevailing practice has been to segregate the new born in common nurseries, from which they are taken to their mothers only at feeding times. The possibility that this uniquely American practice, presumably designed for efficient handling of infants by assembly-line methods, might be overlooking some age-old instincts of mothers who want their babies near them has been engaging the attention of pediatricians, obstetricians, and others. Several institutions have recently begun to provide rooming-in accommodations on either an experimental or established basis. These include the Cornelian Center in Detroit¹, The Grace Powell Hospital (Yale University) in New Haven², the George Washington University Hospital in Washington, D.C.,³

the Department of Obstetrics at Jefferson Hospital, Philadelphia⁴, Permanente Hospital in Oakland, California⁵, and a small hospital in Los Alamos, New Mexico⁶. The present review deals with some of the theoretical and clinical considerations appearing in the recent literature on this subject.

Theoretical. The psychological needs of infants have been emphasized by Gesell⁷, Aldrich⁸, Frank⁹ and others. The importance of having the newborn baby near its mother for purposes of comfort, warmth, and satisfaction has been recognized. Early establishment of continuous and intimate relationship between mother and infant is regarded as important for the acquisition of mutual confidence and freedom from tension. Such confidence is too often lacking under present conditions, when mother and baby confront each other as virtual strangers on their return home from a maternity institution.

Early establishment of a natural feeding pattern is also regarded as important for the newborn infant. Such patterns have been found to vary widely among individual babies. There is a growing tendency among pedia-

tricians to encourage the feeding or nursing of the newborn on the infant's own "demand," rather than to impose a rigid feeding schedule. Proponents¹⁴ of "self-demand" feeding have found that when the plan is instituted early in the infant's life, an individual and fairly regular feeding pattern or schedule is assumed by the infant within a period of 6 to 8 days.

It is claimed that the rooming-in plan makes the satisfying of these desirable aims feasible¹⁵.

Arrangement. Hospital Planning. The physical arrangements necessary for an institutional rooming-in plan may vary widely. Ideally, each mother should, as in domiciliary obstetrics, be quartered in her own room with her infant's bassinette near by. It is safe, however, to set up bedside bassinets in fairly large lying-in wards, as experience abroad has shown. But small units, accommodating not more than 6 mothers, are preferred⁸. A prime requisite is adequate plumbing in the form of running water and, where possible, toilet facilities, located within each unit for the exclusive use of its occupants.

Organization of supplies for rooming-in care may also vary widely. In general, it is advantageous to individualize such material for each patient, arranging it in equipment placed by her own bedside.

Nursing Staff Organization. It has been found desirable to assign nurses to the combined care of small groups of mothers and their infants, rather than to divide their obstetric and pediatric responsibilities. For this, training and skill in both obstetric and pediatric nursing are obviously mandatory. It also goes without saying that mature understanding and sympathy are as important for the successful nursing direction of a rooming-in enterprise as they are for any nursing activity.

Selection of Patients. At the present

time, the best candidates for rooming-in are obviously those women who, having made the acquaintance of the principles and aims of the method, desire it. By and large, this has been found to include a majority of women so informed. It has been suggested that the plan appeals most strongly to those women who have a natural maternal desire to nurse their infants at the breast⁷. The patient's and her family's cooperation is required in assenting to the strict limitation of visiting privileges deemed necessary for the safe operation of the plan in hospital practice.

Visiting Privileges. Practice, both here and abroad has favored limitation of visitors to the husband exclusively. This limitation has been designed not only for the safety and comfort of the mother and infant, but also for the purpose of giving the husband an early acquaintance with his child, and enlisting his interest in participating in its care.

Routine. The newborn infant may be placed in its bassinette at the mother's bedside directly upon its arrival from the delivery room, or following a preliminary period of observation elsewhere. The nurse assigned to the mother and her infant is responsible for daily or periodic observations and attentions, these including such procedures as weighing the baby, taking its temperature and dressing the cord. The nurse's responsibility includes indoctrinating the mother in all of these procedures, as well as instructing her in how to feed the infant and change its diapers. The carrying out of all routines is transferred to the mother as soon as possible.

The initial and subsequent examinations of the infant by the pediatrician are carried out in the presence of and for the instruction of the mother.

Self-demand feeding is permitted and encouraged. Under natural cir-

cumstances the infant is put to breast early, and as often thereafter as it seems hungry. Where additional or artificial feedings are indicated, prepared formulas are brought to the mother to feed to her infant.

Results. Institutions^{2,7,8,9,11} in which the rooming-in plan has been under trial report advantages for all concerned in the enterprise.

For the infant, feeding and hygiene problems appear to have been more satisfactorily met under this plan than was possible in the same institution under previous plans. A higher incidence of breast feeding is said to have been encouraged, and a more satisfactory performance of this natural function attained. The incidence of infection, both dermal and enteric, has been reduced.³

For the mother, it is claimed that the plan provides both psychological⁶ and physical benefits. Her instinctive desire to be near her infant, and to care for it, is satisfied. She gains an early confidence in her ability to provide such care. Her rest is undisturbed by unnecessary visitors. Despite the company of other mothers and their infants in the same unit, her surroundings are restful, because the infants, being well fed, are quiet.¹³

For the hospital administration and its nursing staff, it has been observed that rooming-in simplifies the problem

of attending mothers and their infants. Because the mothers are early entrusted with much of the care of their babies, demands upon the time and services of the nursing staff are reduced.¹⁰ Curtailment of visitor traffic similarly and further reduces demands upon nursing and administrative staffs.

Comment. The reviewers venture the prediction that rooming-in will have a growing appeal for the prospective mothers of this country. Those¹³ who have re-discovered its virtues have drawn attention to the neglect of some very homely, but very important values in the conduct of our maternity institutions. It is to be expected that the subject, already introduced to the public by the lay press, will be further popularized. The resultant demands upon our maternity hospitals may then be widespread, inasmuch as over three-fourths of the births in this country now occur in such hospitals.¹² Moreover, the demands may entail structural alterations in many hospitals. These cannot be evaded by recommending a return to domiciliary obstetrics, inasmuch as the present preference for institutional obstetric services has, in itself, been mainly the result of economic pressures. Rooming-in, therefore, is a subject which is likely to require more serious attention than its simple and homely connotations would suggest.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 20, 1948

The Effect of Adrenalectomy on the Blood Pressure of Rats Subjected to Auditory Stimulation. S. McDONALD McCANN, M.D., ALAN B. ROTHBALLER, M.D., ELEANOR H. YEAKEL, Ph.D., and HENRY A. SHENKIN, M. D. (Harrison Dept. of Surg. Research, Univ. of Penna., and the Wistar Institute of Anatomy.) It has been shown in previous experiments that the majority of rats subjected to prolonged auditory stimulation develops an elevation of blood pressure. It seemed possible that the experimental procedure constituted a chronically alarming stimulus and produced the increase in blood pressure through a pituitary-adrenal cortex mechanism. As a step toward testing this hypothesis, 7 rats made hypertensive by prolonged air-blasting and a group of 4 control animals were subjected to adrenalectomy and subsequent replacement therapy. Air-blasting of the experimental animals was continued to prevent a fall of blood pressure from cessation of the auditory stimulus and blood pressures were taken frequently by the tail plethysmograph method throughout the experiment. Following adrenalectomy all the animals were maintained on 1% sodium chloride in the drinking water until their pressures had stabilized at a low level. Then restoration therapy consisting of 1 cc. of cortical extract (Eschatin) intramuscularly per day per animal was instituted. Before adrenalectomy the average blood pressure of the experimental animals was 162 mm. and that of the controls 125 mm. of Hg. On removal of the adrenals the blood pressures of the experimentals and controls fell to sub-

normal levels, i.e., 108 and 97 mm. of Hg. respectively. Cortical extract administration was followed by a rise of blood pressure to 125 mm. in the experimental animals and to 112 mm. in the controls. Thus it can be seen that the blood pressures of both groups of animals dropped to subnormal levels following adrenalectomy. Restoration therapy raised the blood pressures of the animals to approximately normal levels, but in no instance was the elevated blood pressure of the rats being air-blasted restored. These results are statistically significant. It is suggested that the adrenal cortex mediated the elevation of blood pressure occurring during prolonged auditory stimulation.

Experimental Differentiation of Pathogenesis of Serum Sickness, Glomerular Nephritis, Rheumatic Fever, and Periarthritis Nodosa. WILLIAM E. EHRLICH, M.D., CAROLYN FORMAN, M.D., and JOSEPH SEIFTER, M.D. (Univ. of Penna. Dept. Grad. Path., Phila. Gen. Hosp., and Wyeth Inst.) Rabbits received 1 or 2 intravenous injections of 10 cc. of horse serum per kilo and were sacrificed after various intervals from 3 to 34 days following the first injection. A single injection regularly caused round-cellular infiltration and proliferation especially in heart and lungs closely resembling the lesion in human serum sickness. As they were present 3 days after injection, they were interpreted as direct in nature. Of the animals killed after 14 days, 44% revealed a proliferative arteritis showing all the allergic qualities recently described by Goddard.

This lesion was interpreted as a delayed or subacute Arthus phenomenon due to an antigen-antibody reaction during the process of fixation of antibody while antigen was still in circulation. This reaction closely resembled the lesion of human rheumatic fever. Of the animals killed after a second injection, 50% revealed a necrotizing arteritis, *i.e.*, an acute Arthus phenomenon due to a sudden reaction of large quantities of antigen with abundant antibody previously fixed in the vascular tissue. This lesion was the same as that of human periarteritis. There were also at least 2 types of glomerulonephritis, namely an extracapillary one brought about by an acute allergic reaction and occurring only after a second injection, and an intracapillary one, which in our animals was seen only 14 days after a single injection and therefore should be explained at least in part by a subacute allergic reaction. However, Hawn and Janeway saw it in a considerable number of animals 7 days after a single injection. This observation suggests that there may be a direct glomerulonephritis as well.

A Rationale of Salicylate Treatment of Experimental Serum Sickness. CAROLYN FORMAN, M.D., JOSEPH SEIFTER, M.D., and WILLIAM E. EHRLICH, M.D. (Univ. of Penna. Dept. Grad. Path., Phila. Gen. Hosp. and Wyeth Inst.) Though the effectiveness of massive doses of salicylates in rheumatic fever has not been established, it is agreed that they are toxic and they suppress blood coagulation, blood sedimentation and antibody titration. As human material doesn't lend itself to an investigation of this problem, rabbits were given serum disease, and some rabbits were subjected to salicylate treatment. Others received a drug that interfered with blood coagulation (dicoumarol). As the toxic effect and the suppression of antibody

titration suggested an alarm reaction, *i.e.*, destruction of antibody forming lymphoid cells, a last series of rabbits received colchicine. It was found that the rabbits tolerated a salicylate level of only 200 to 300 gamma per cc. This did not produce significant suppression of precipitin titration or any of the tissue changes induced by horse serum, but it caused interference with coagulation and a significant depression of the weight of the thymus showing that 200 to 300 gamma per cc. in rabbits have an alarm reacting effect. Dicoumarol interfered with coagulation and produced a considerable depression of precipitin titration, but did not depress the lymphoid tissues or any of the cellular reactions induced by horse serum. Colchicine finally caused marked depression of the weight of the thymus as well as of precipitin titration, and it also abolished the subacute allergic arteritis which is generally believed to be the experimental equivalent of the lesion of human rheumatic fever. These observations seem to show that the massive doses of salicylates used in rheumatic fever have an alarm reacting effect, and that the development of allergic arteritis may be suppressed, if a treatment that destroys lymphatic tissue is applied during the period of antibody formation preceding the antigen-antibody reaction that causes the arteritis.

Retinal Action Potentials of Photoreceptor Cells and the Discharge of Nerve Impulses in Their Axones. H. K. HARTLINE, M.D. (Johnson Research Foundation, Univ. of Penna.) Single ommatidia, containing 10 to 15 retinula cells with $\frac{1}{4}$ mm of their attached axones, were isolated in the compound eye of *Limulus*. An oscillograph and D.C. amplifier were used to record the slow changes in electrical potential between one electrode placed

on the piece of cornea to which the distal ends of the retinula cells were attached and another electrode on the proximal end of the ommatidium where the nerve strand emerged (retinal action potential). Simultaneously, impulses in the nerve strand were recorded by another amplifier and oscillograph. Upon illumination, the corneal electrode became more negative relative to the proximal electrode; at the same time impulses were discharged in the nerve strand. There was a rough parallelism between the rise and fall of the retinal action potential and the frequency of discharge of impulses; different intensities of stimulation and different conditions of adaptation had comparable effects on both responses. Closer analysis, however, showed that the parallelisms were far from exact; in many preparations it was possible to elicit large changes in the impulse discharge with only very slight concomitant retinal action potentials. It is not yet possible to decide whether the local currents accompanying the retinal action potential may be considered the direct cause of the discharge of nerve impulses by the photoreceptor cells.

CORRECTION

On pages 172 and 173 of the February 1948 issue, in the first article on "Study of Fixed Tissue Sections of Sternal Bone Marrow Obtained by Needle Aspiration" by Drs. Anstin Weisberger and Robert W. Heinle, the photomicrographs on page 173 belong with the legend on page 172, and vice versa.

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BOOK REVIEWS AND NOTICES

HORMONES AND BEHAVIOR. By FRANK A. BEACH, Prof. of Psychology, Yale Univ. Pp. 368. New York: Paul B. Hoeber, 1948. Price, \$6.50.

This book represents an effort to evaluate, in various phyla including man, the influence of endocrine function upon behavior, in the light of experimental evidence. The literature is extensively reviewed (approximately 750 references), but the conclusions quoted are sometimes so conflicting that the general effect upon the reader is often one of slight bewilderment. The behavioral responses examined in the 14 chapters include those related to sexual and parental functions, migration, general locomotor activity, learning and territory defense. The style is wordy and is not conducive to easy reading; simple and obvious points are often belabored—"It is obvious that much of an animal's behavior depends upon the possession of a normal complement of organs and organ systems, well constructed and functionally efficient effector and receptor mechanisms, the attainment of normal growth, etc." (Page 255.) The book will probably be of interest chiefly to students of psychology.

E. R.

BLOOD PRESSURE AND ITS DISORDERS, INCLUDING ANGINA PECTORIS. By JOHN PLESCH, M.D., formerly Prof. of Internal Medicine, Univ. of Berlin. 2nd ed. Pp. 307; 125 figs. Balt.: Williams & Wilkins, 1947. Price, \$6.00.

This book represents nearly 50 years of work, study and thought by the author in the general field of circulation. It is restricted, as he states, to those matters of which he has personal experience, and is not a review. A method for graphically recording the blood pressure is given in detail, along with a careful analysis of the presumed significance of the records so obtained. Indeed, herein lies the chief appeal to the student and investigator, who will find much that is stimulating. However, the reader is unlikely to agree with the author on all points, and the lack of correla-

tion with more modern studies is undoubtedly a weakness. The bibliography is not large, and contains more references prior to 1920 than since that year. The book is recommended for libraries and for advanced students who already have some knowledge of the field.

J. G.

THE RH FACTOR IN THE CLINIC AND THE LABORATORY. Edited by JOSEPH M. HILL, M.D., and WILLIAM DAMESHEK, M.D. Special issue No. 2 of *Blood, The Journal of Hematology*. Pp. 192; 25 ills. New York: Grunc & Stratton, 1948. Price, \$4.25.

This volume comprises 13 presentations with group discussions and a preface by the senior editor. These papers were presented at the Dallas-Mexico City Rh Conference of November, 1946. The symposium concerns various aspects of the Rh factor, including an excellent "Survey" by Philip Levine, discussion of "Rh Genotypes" by R. R. Race (London), a review of "Hemolytic Mechanisms" by Dameshek, "Variations in Erythroblastosis Fetalis" by Bruce Chown (Manitoba), and "Treatment of Erythroblastosis Fetalis" by Harry Wallerstein. The volume is a useful historical document and reference source for specialists and students in this important, complex field.

T. F., Jr.

TREATMENT OF SOME CHRONIC AND "INCURABLE" DISEASES. By A. T. TODD, O.B.E., M.B. (EDIN.), M.R.C.P. (LOND.). 2nd ed. Pp. 324. Balt.: Williams & Wilkins, 1947. Price, \$7.00.

This book contains a few useful ideas, but it is difficult to separate them from the theories, speculations and opinions of the author. It is hard to believe that he can cure such conditions as diabetes mellitus, epilepsy, asthma, hyperthyroidism, constipation, colitis, arthritis and a host of other conditions by correcting the underlying disturbances, which almost invariably turn out to be ethmoid infection, duodenal infection and hepatic dysfunction.

H. H.

PHYSICS FOR THE ANESTHETIST. By R. R. MACKINTOSH, M.A., M.D., F.R.C.S., D.A., Nuffield Prof. of Anæsthetics, Oxford, and W. W. MUSKIN, M.A., M.B., B.S., D.A. Pp. 235; 431 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$7.50.

THE authors have gathered together in this small volume "such applications of physics to anesthetics as we meet with during routine work." The occasional oversimplification in presentation can be excused because of the purpose of the book, namely to "supply answers to straightforward questions."

The text is lucidly written, cleverly illustrated, and the format is attractive. It should form a valuable addition to an anesthetist's library. R. D.

RECENT ADVANCES IN SEX AND REPRODUCTIVE PHYSIOLOGY. By J. M. ROBSON, M.D., D.Sc. (LEEDS), F.R.S.E., Reader in Pharmacology, Guy's Hospital Medical School, Univ. of London. 3rd ed. Pp. 336; 69 ills. Phila.: Blakiston, 1948. Price, \$5.75.

THIS edition deals more with the current physiologic concepts of sex and reproduction than with clinical considerations. Major emphasis is placed upon the female reproductive system. The general metabolic effects of the sex hormones receive little attention. The book will be of more interest to students than to practitioners.

E. R.

CALCIFIC DISEASE OF THE AORTIC VALVE. By HOWARD T. KARSNER, M.D., and SIMON KOLETSKY, M.D. Pp. 111; 24 ills. Phila.: J. B. Lippincott, 1947. Price, \$5.00.

THIS monograph presents a survey of calcific disease of the aortic valve. The authors' stated purpose is to determine whether this disease is of inflammatory or degenerative origin; they conclude that, with only rare exceptions, it is the result of rheumatic cardiac disease. The text is heavy with much statistical analysis, which is better understood as presented in 35 Tables. Pathological anatomy is discussed in detail, with the aid of some good illustrations. This work will primarily interest pathologists or research workers in cardiac disease. However, clinicians might profit from the chapters on Clinical Features and Summary, which comprise about the last third of the book. H. Z.

STEREOSCOPIC ATLAS OF NEURO-ANATOMY. By H. S. RUBINSTEIN, M.D., Ph.D., Director, Alfred Ullman Laboratory for Neuro-Psychiatric Research, Sinai Hospital, Baltimore, and C. L. DAVIS, M.D., Prof. of Anatomy, School of Medicine, Univ. of Maryland. Pp. 20; 43 ills. New York: Grune & Stratton, 1947. Price, \$10.00.

THE plates of the atlas are printed on separate stiff cards measuring 7 by 9 inches. On the lower part of each card are two photos side by side, which are to be viewed through an ordinary stereoscopic viewer. On the upper part of each card is a labeled diagram explanatory of the pictures below. Accompanying the plates is a pamphlet that gives an outline of the methods of dissection of the brain used in displaying the structures shown on the plates. The plates and pamphlet are contained in a cardboard box.

The first 5 plates show developmental stages and are followed by 3 plates of meninges and 4 of external views. The deeper dissections shown in the last dozen plates are the most interesting since they display the skillfulness of the dissector. The authors have their students use the plates as the actual dissection proceeds and later the students use the plates for reference to earlier stages of the dissection which have been destroyed in the further course of the dissection. For anyone having some first-hand acquaintance with the human brain the method has great merits. It allows the repetition and review which are so important in acquiring a lasting knowledge of brain structure. At any time, with these plates, one can quickly refresh one's memory without the necessity of specimens. Also the study of these plates may excite interest in the viewer to make dissections for himself. W. A.

A TEXTBOOK OF BACTERIOLOGY. By THURMAN B. RICE, A.M., M.D., Prof. of Bacteriology and Public Health, Indiana Univ. School of Medicine. 4th ed. Pp. 603; 126 ills. Phila. and London: W. B. Saunders, 1947. Price, \$6.50.

As compared with the previous edition, this one has an increase of 43 pages; 2 new chapters, 1 on antigens and antibodies, and the other dealing with chemotherapeutic and antibiotic agents; and 1 additional minor section in the Appendix dealing with the classification of microorganisms. The subject matter is quite similar except for the occasional addition of new material in the more recent edition. H. M.

NEW BOOKS

Skeletal Tuberculosis. By VICENTE SANCHIS-OLMOS, M.D., Ass't Director, Instituto Nacional de Reeducacion de Invalidos de Carabanchi Bajo, Madrid. Translated by JOHN G. KUHN, M.D., Pp. 261; 104 ills. Balt.: Williams & Wilkins, 1948. Price, \$5.00.

The Epithelia of Woman's Reproductive Organs. By GEORGE N. PAPANICOLAOU, M.D., Ph.D., Prof. of Clinical Anatomy, Cornell Univ. Medical College, HERBERT F. TRAUT, M.D., Prof. of Obstetrics and Gynecology, Univ. of California Medical School, and ANDREW A. MARCHETTI, M.D., Assoc. Prof. of Obstetrics and Gynecology, Cornell Univ. Medical College. Pp. 53; 24 ills. New York: The Commonwealth Fund, 1948. Price, \$10.00.

Medicolegal Problems. Edited by SAMUEL A. LEVINSON, M.D., Ph.D., Univ. of Illinois College of Medicine, for The Committees of the Institute of Medicine and the Chicago Bar Association. Pp. 255; 6 ills. Phila.: J. B. Lippincott, 1948. Price, \$5.00.

Atlas of Plastic Surgery. By MORTON I. BERSON, M.D., Formerly Director Department of Plastic and Reconstructive Surgery, Downtown Hospital and Pan-American Clinic, New York. Pp. 304; illustrated. New York: Grune & Stratton, 1948. Price, \$15.00.

Recent Progress in Hormone Research. Edited by GREGORY PINCUS. Proceedings of the Laurentian Hormone Conference, Vol. II. Pp. 427; illustrated. New York: Academic Press, 1948. Price, \$8.00.

Psychiatry for the Pediatrician. By HALE F. SHURLEY, M.D., Assoc. Prof. of Pediatrics and Psychiatry, Stanford Univ. School of Medicine. Pp. 442. New York: Commonwealth Fund, 1948. Price, \$4.50.

Psychosocial Medicine. A Study of the Sick Society. By JAMES L. HALLIDAY, M.D., D.P.H. Pp. 278. New York: W. W. Norton, 1948. Price, \$3.50.

Heart. By ALDO A. LUISADO, M.D., Instructor in Physiology and Pharmacology, Tufts College Medical School. Foreword by HERMAN L. BLUMGART, Prof. of Medicine, Harvard Medical School. Pp. 653; 352 figs. Balt.: Williams & Wilkins, 1948. Price, \$10.00.

Textbook of Endocrinology. By HANS SELYE, M. D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada). Preface by BERNARDO A. HOSSAY. Pp. 914; illustrated. Montreal, Canada: Universite de Montreal, "Acta Endocrinologica", 1947. Price, \$12.50 plus mailing charges.

"NEW EDITIONS"

Diseases of the Skin. By OLIVER S. ORMSBY, M.D., Rush Prof. of Dermatology Emeritus, Univ. of Illinois, and HAMILTON MONTGOMERY, M.S., M.D., Ass't Prof. of Dermatology and Syphilology, Mayo Foundation, Univ. of Minnesota. 7th ed. Pp. 1465; 764 ills., 18 in color. Phila.: Lea & Febiger, 1948. Price, \$18.00.

Pathological Histology. By ROBERTSON F. OGILVIE, M.D., F.R.C.P. (Edin.), F.R.S.E., Lecturer in Pathology and Assistant in Forensic Medicine, Univ. of Edinburgh. 3rd. ed. Pp. 459, 260 ills., in color. Balt.: Williams & Wilkins, 1947. Price, \$10.00.

THE third edition, companion to a standard textbook of pathology, continues to deserve the eminence attained by its predecessors. While it maintains the plans and purpose of the previous issues, the author has largely rewritten the text. The illustrations have been improved both by substitutions and additions. The new subjects and plates materially extend the range of pathological processes. The book is recommended to students and interested physicians desiring a quicker view of pathological histology. II. B.

Treatment in General Practice. By HARRY BECKMAN, M.D., Prof. of Pharmacology, Marquette Univ. School of Medicine. 6th ed. Pp. 1129. Phila.: W. B. Saunders, 1948. Price, \$11.50.

IN ORDER to keep abreast with the newer developments, this new edition appears after an interval of only two and one-half years. The material is presented as in former editions in the author's terse and often whimsical style, approaching management of disease from the practical as well as the scientific point of view. A number of new sections have been added, notably one on reactions to penicillin. The bibliography is well chosen with many references from very recent literature. The book is an excellent starting point in treatment for internists as well as general practitioners who will find it useful and worthwhile. E. L.

Poisons, Their Isolation and Identification. By FRANK BAMFORD, B.Sc., Late Director of the Medico-Legal Laboratory, Cairo. Revised by C. P. STEWART, M.Sc., Ph.D., Univ. of Edinburgh. 2nd ed. Pp. 304; 23 ills. Phila.: Blakiston, 1947. Price, \$5.00.

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